Medication Adherence Outcomes in Elderly Patients with Hypertension and Chronic Kidney Disease: a Geographical Approach

by

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DEDICATION

I dedicate this dissertation to my husband Lu Wang, for all his love and support.

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LIST of ABBREVIATIONS AND ACRONYMS

AASK – African American Study of Kidney Disease

ACEIs – angiotensin-converting enzyme inhibitors

ACP – American College of Physicians

ACR – albumin-creatinine ratio

ACS – American community Survey

AFIB – atrial fibrillation;

AIC –Akaike Information Criterion

AIDS – acquired immunodeficiency syndrome

AMI – acute myocardial infarction;

ARBs – angiotensin-receptor blockers

ASHD – atherosclerotic heart disease

AT1R – angiotensin type 1 receptor

AT2R – angiotensin type 2 receptor

BIC – Bayesian Information Criterion

BUN – blood urea nitrogen

CABG – coronary artery bypass grafting;

CCI – Charlson comorbidity index

CHF – congestive heart failure

CHF – congestive heart failure

CIBIS-II – cardiac insufficiency bisoprolol study II

CKD – chronic kidney disease

CKD-MBD – chronic kidney disease–mineral bone disorder

CMS – Centers for Medicare & Medicaid Services

CRT-D –cardiac resynchronization therapy with defibrillator devices.

CVA/TIA – cerebrovascular accident/transient ischemic attack

CVD – cardiovascular disease

DALYs – Disability Adjusted Life Years

ESRD – end-stage renal disease

FIPS – Federal Information Processing Standard

GFR – glomerular filtration rate

GWR – geographically weighted regression

HCPCS – Healthcare Common Procedure Coding System

HMO – Health Maintenance Organization

HRSA – Health Resources and Services Administration

HTN – hypertension

ICD – implantable cardioverter defibrillators

ICD-9-CM – International Classification of Diseases, Ninth Revision, Clinical Modification

IDNT – Irbesartan Diabetic Nephropathy Trial

IRB – Institutional Review Board.

K/DOQI – Kidney Disease Outcomes Quality Initiative

LIS – Low-income Subsidy

MA-PD – Medicare Advantage prescription drug

MDRD – modification of diet in renal disease study

MERIT-HF – Metoprolol Controlled-Release Randomized Intervention Trial in Heart Failure

MSP – Medicare Saving Programs

MUAs – medically underserved areas

NDC – national drug code

NHANES – National Health and Nutrition Examination Survey

PAD – peripheral arterial disease

PCI – percutaneous coronary interventions

PCSA – Primary Care Service Area

PDC – proportion of days covered

PDP – Prescription Drug Plans

RAAS – renin-angiotensin-aldosterone system

RAS – renin-angiotensin-system

RCT – randomized controlled trial

REGARDS – Reasons for Geographic and Racial Differences in Stroke study

RRI-CKD – Renal Research Institute Chronic Kidney Disease study

SAFs – Standard Analytical Files

SCA/VA – sudden cardiac arrest and ventricular arrhythmias;

SENIORS – Seniors with Heart Failure trial

SSA – Social Security Administration

SSI – Supplemental Security Income

USRDS – United States Renal Data System

USRDS ADR – United States Renal Data System Annual Data Report

VIF – variance inflation factor

ABSTRACT

OBJECTIVES: Chronic kidney disease (CKD) patients with uncontrolled blood pressure are at high risk of cardiovascular events, hospitalization, and mortality. There is limited research evaluating utilization patterns of anti-hypertensives in hypertensive CKD patients. This study aims to assess anti-hypertensives use, particularly, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) in the United States, and explore contextual and individual risk factors of treatment compliance.

METHODS: Hypertensive CKD patients were selected using Medicare 5% sample claims data from the United States Renal Data System (USRDS) databases (2006-2013). We included patients who diagnosed with hypertension and CKD, and followed them from Jan 1, 2008 to Dec 31, 2013. We first investigated medication treatment patterns among incident CKD patients. We then performed time-dependent survival analyses to evaluate long-term benefits of being adherence to ACEIs/ARBs. Medication adherence in this study was measured by proportion days covered (PDC). Lastly, we used geographically weighted regression model (GWR) to explore risk factors of medication adherence.

RESULTS: Approximately 50% of incident hypertensive CKD patients received guideline-recommended ACEIs/ARBs after their first diagnosis of CKD. Anti-hypertensive regimens including ACEIs/ARBs and statins yielded better CKD outcomes than regimens without these drugs. Additionally, continuously being adherent to ACEIs and ARBs was associated a significant decline in risk of end-stage renal disease (ESRD) and mortality in

long run. However, only 61% of hypertensive CKD who used ACEIs/ARBs had good medication compliance (PDC ≥80%). Patients residing in the Northeast region and the Midwest region demonstrated better adherence than those residing in the Southern United States. Availability of primary resources, neighborhood deprivation status, and coverage of Part D Low-income Subsidy (LIS) were factors related with medication adherence. Geographically varied association between contextual characteristics and adherence were displayed by maps.

CONCLUSIONS: Utilization of guideline-recommended ACEIs/ARBs is suboptimal in elderly patients with hypertension and CKD in the United States, although they had significant long-term benefits on CKD outcomes. Adherence to ACEIs/ARBs is geographically differentiated across the United States. Contextual and individuals risk factors identified in this study are helpful to design population-based strategies in a local area to promote medication compliance, from a population perspective.

Chapter 1

INTRODUCTION

1.1 Statement of the problem

Approximately 15% of adults in the United States may have CKD with varied seriousness levels [1]. Aging adults are particularly at high risk of CKD, as over one-third of elderly adults have CKD, either spots estimates of Glomerular Filtration Rate (GFR) less than 60 ml/min/1.73m^2 or albumin-creatinine ratio (ACR) $\geq$ 30 mg/g [1]. Medicare spending for elderly adults with CKD represents 20% of total Medicare spending [1].

Pharmacological therapies and lifestyle changes can slow down CKD progression to ESRD, when kidney failure occurs and dialysis or kidney transplant is required[2]. Hypertension is a previously established risk factor for CKD progression. Although about 74 percent of CKD patients have hypertension, only 28 percent of them achieve blood pressure under-controll[1]. ACEIs and ARBs are guideline-recommended blood pressure lowering agents for patients with hypertensive CKD. They have substantial effects on the renin-angiotensin-aldosterone (RAA) hormonal system. Previous studies showed low adherence to ACEIs/ARBs related with increased risk of progression to ESRD among patients with hypertensive CKD[3,4].

A major knowledge gap exists in understanding the relationship between access to health care and use of ACEIs/ARBs in elderly patients with hypertensive CKD. No study has systematically modeled how individual and contextual factors affect ACEIs/ARBs adherence

by incorporating geographical variation across continuous space. Meanwhile, limited research has compared the effect of different pharmacological treatment strategies in hypertensive CKD. Additionally, there is lack of a model that can more accurately assess the effect of ACEIs/ARBs on the progression of CKD and mortality by accounting for the time varying medication consumption. This knowledge is critical to develop effective interventions for elderly patients with hypertension and CKD. It is our hypothesis that patients' adherence to ACEIs/ARBs is critical to CKD progression and mortality, and it is influenced by the barriers of accessibility to health care and availability of health care, such as residing in Medically Underserved Areas (MUAs) and numbers of physicians per population.

1.2 Nature of the Study

This retrospective cohort study aimed to explore the predictors of medication use behaviors, and examine the association between medication use behaviors and health care outcomes for elderly hypertensive patients with CKD in the United States. We applied a theoretical framework modified from health services behavioral research models to address our research questions.

1.3 Study Aims

The purpose of this study is to provide pharmacological treatment strategies to delay the progression to ESRD for elderly patients with hypertensive CKD in the United States, and develop and use of methodology to measure and model geographically varied predictors of medications adherence. We refined the spatial methodologies for use in future medication use/renal disease studies in the United States. Additionally, the time-dependent medication use behavior model we developed in this study can be used in other chronic diseases. Our

central hypothesis was that elderly patients with hypertensive CKD who had better access to healthcare and healthcare availability were more likely to be adherent to their prescribed ACEIs/ARBs, and further demonstrated better CKD treatment outcomes. The rationale for the proposed study was to identify contextual and individual factors that related with poor adherence to ACEIs/ARBs, and accurately model how ACEIs/ARBs consumption were associated with CKD progression and mortality. The results of our study will provide important information on physicians' prescribing strategies aimed at improving the effectiveness of treatment and delaying CKD progression to ESRD in elderly hypertensive patients. Our main data was the Medicare 5% sample claims from the USRDS databases (2006-2013). In this study, we tested our central hypothesis with the following three aims:

Aim 1 Compare the effects of different pharmacologic therapies on CKD outcomes for hypertensive CKD in Medicare Part D enrollees.
Aim 2 Examine the effects of ACEIs/ARBs adherence on CKD progression and mortality.
Aim 2 Model ACEIs/ARBs adherence as a function of individual and contextual factors among aged hypertensive patients with CKD in the United States.

These aims yielded the following outcomes: In aim 1, we described the anti-hypertensive therapies hypertension patients received when they first diagnosed with CKD, and compare effects of these different regimens. In aim 2, we explored how ACEIs/ARBs adherence delays progression to ESRD and mortality, and provided evidence to encourage increased use of ACEIs/ARBs in hypertensive patients with CKD. In aim 3, we examined geographic variation in medication adherence to ACEIs/ARBs among aged hypertensive patients with CKD in the United States, and explored the relationship between individual characteristics, contextual characteristics and medication adherence.

1.4 Significance of the Study

The National Kidney Foundation Clinical Practice Guidelines recommend the target blood pressure for hypertensive patients with CKD should be <130/80mm Hg. There are two main treatment goals of antihypertensive therapy in CKD: (1) lower blood pressure and (2) block the RAA hormonal system using ACEIs or ARBs[5]. ACEIs and ARBs are recommended as the preferred agents for blood pressure control in all diabetic CKD patients and nondiabetic patients with urine ACR ≥200 mg/g, as well as hypertensive patients with mild to moderate kidney dysfunction. Despite the effects of ACEIs/ARBs, that have objectively demonstrated protective effects on the progression of renal insufficiency in several randomized control trial studies[6–8], there is evidence that ACEIs/ARBs are underutilized in hypertensive CKD patients. Less than half of CKD patients used ACEIs/ARBs to control their blood pressure, and the highest ACEIs/ARBs utilization rate was observed in moderate CKD patients[9,10]. Little research has compared different pharmacological treatment strategies for hypertensive CKD patients; evaluated the long-term effects of ACEIs/ARBs on CKD progression to ESRD and mortality; as well as explored risk factors of ACEIs/ARBs adherence.

This contribution is significant because the first step of our research is expected to provide evidence for clinicians when they select pharmacological treatments for elderly patients with hypertension and CKD. Additionally, this study contributes to understanding of how much improvement in healthcare outcomes can be obtained by continuously being adherent to ACEIs/ARBs. Lastly, the major crucial step of our research is expected to find predictors of ACEIs/ARBs adherence and provide helpful information for designing effective interventions. For instance, the contextual factors identified in this study may be helpful for healthcare providers to target on CKD patients at high risk of poor medication compliance.

1.5 Innovation of the Study

To the best of our knowledge, this is the first study that explored geographic varied predictors of ACEIs/ARBs adherence among aged hypertensive CKD patients. We conducted a theoretically grounded analysis to identify contextual risk factors. Unlike global regression model that ignores the connections between geographic areas, the spatial model we used in our study is able to incorporate the spatial autocorrelation when model medication adherence as a function of potential predictors[11,12]. The strength of our study is we are able to provide visualized information, such as maps that reflect geographic differences in the relationship between predictors and medication adherence. Results of our study support the long-term benefits of ACEIs/ARBs, and encourage increased use of ACEIs/ARBs among elderly hypertensive patients with CKD. In addition, we believe our study could help healthcare providers understand the geographic variation of the relationship between predictors and medication adherence. This information is valuable for researchers to design local interventions aiming at improving ACEIs/ARBs use among elderly CKD patients, and support health care policy makers to allocate medical resources within small administrative areas. Furthermore, the proposed research is innovative, as we developed a multivariate Cox regression model with ACEIs and ARBs use as time-varying covariates to assess the long-term benefits of ACEIs and ARBs.

Chapter 2

LITERATURE REVIEW

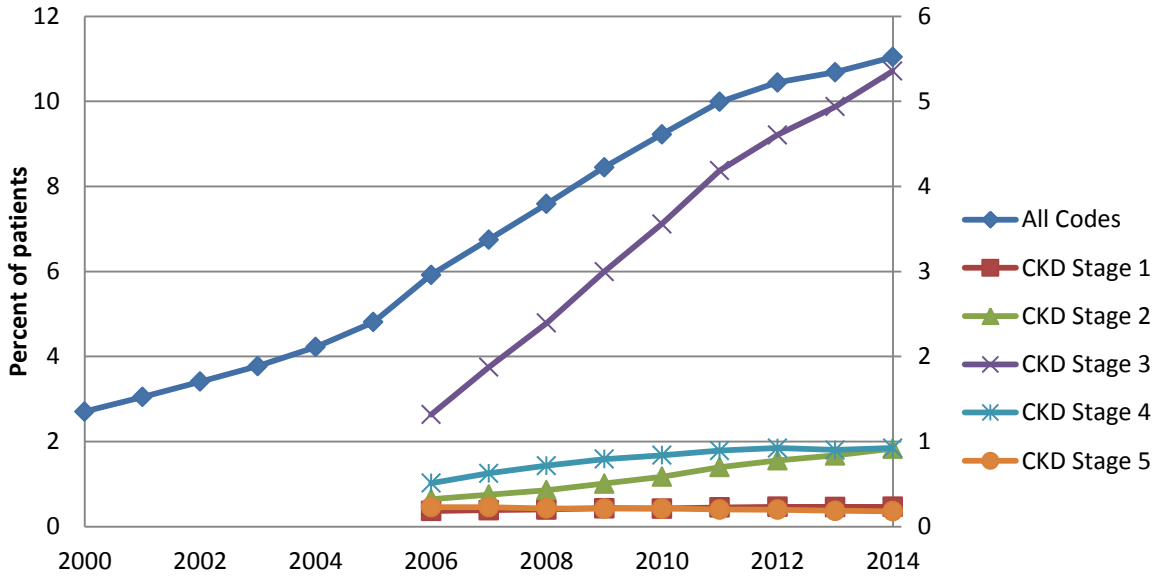
2.1 Epidemiology and economic burden of CKD

CKS is becoming a greater priority for global public health and healthcare[13,14]. The prevalence of CKD in the general population varied widely across regions, from 5.8% in Poland to 13.1% in the United State[13]. Findings from the Global Burden of Disease study 2010 showed numbers of deaths from chronic kidney disease in 2010 was 735.6 million, 82.3% more than in 1990. This caused the CKD increased from the 27th cause of death to the 18th cause of death in the world over the two decades[15]. In term of the overall disease burden, in 2010, CKD accounted for a total of 21.51 million disability-adjusted life years (DALYs)—about 0.85% of global DALYs, and a 51.7% increase from 1990[16].

Old adults have a markedly higher risk of developing CKD worldwide[17]. For example, by analyzing data from the National Health and Nutrition Examination Survey (NHANES), 2011-2014, researchers found one-third of NHANES participants aged 60 and older had CKD, compared with 7% of those aged 20-39 and 11% of those aged 40–59[1]. Figure 2-1 shows the trend of prevalence of recognized CKD in Medicare beneficiaries by CKD stage. Overall, the CKD prevalence had gradually increased over the past decade, from 2.7% in 2000 to 11% in 2014[1]. Meanwhile, total Medicare spending on elderly patients with CKD

was increased steadily from 7.4 billion in 2000 to 52.8 billion in 2014. The fastest growing occurred in 2006-2007, the period that Part D program launched. This increased spending may because of the growing prevalence of CKD, earlier detection of CKD, increased access to prescription drugs, as well as improved identification and reporting using claims data.

Figure 2-1 Trends in prevalence of recognized CKD, overall and by CKD stage, among Medicare patients aged 65+, 2000-2014



Adopted from USRDS annul data report 2016. Distribution of the overal CKD prevalence, visualized by a blue curve (the points drawn to the scale of the vertical axis on the left), and four curve of the CKD prevalence by stage (the points blue drawn to the scale of the

CKD is generally a progressive and irreversible disease, which has been categorized into five stages based on the level of kidney function. CKD patients who progress to ESRD, also

known as kidney failure, need the initiation of kidney replacement therapy, either dialysis or a kidney transplant, to stay alive. Global variations in ESRD incidence and prevalence were observed in international comparison studies[14]. Taiwan, the Jalisco region of Mexico, and the United States had the highest incidence of treated ESRD, at 455, 421, and 370 per million people[1]. In terms of the prevalence of treated ESRD, Taiwan ranked the first, followed by Japan and the United States.

The time scale of CKD progression is varied across populations. The rate of decline in renal function is influenced by several factors including the cause of CKD, CKD stage at the time of diagnosis, and type of intervention received[18–21]. A longitudinal cohort study found that 1.1% of patients with stage 2 CKD developed ESRD within a 5-year observation period, compared to 1.3% in stage 3 CKD and 19.9% in stage 4 CKD[22]. Meanwhile, the mortality rate was 19.5%, 24.3% and 45.7% for patients with stage 2, 3, and 4 CKD respectively. Death from cardiovascular diseases and diabetes is competing risk of progression to kidney failure.

Globally, CKD and its consequent ESRD are associated with substantial adverse impacts on individual utility and social welfare, including medication expenditures and loss of working time due to disability and absenteeism. According to the United States Renal Data System Annual Data Report 2016 (USRDS ADR), total Medicare expenditures for CKD rose to $52.8 billion in 2014. Even though only 11% of elderly Medicare population had been diagnosed with CKD, they accounted for 21% of total Medicare expenditures in 2014[1]. With regard to ESRD, total Medicare expenditures for ESRD reached 32.8 billion in 2014, 3.3% higher than 2013. In term of indirect cost, CKD and its complications caused a significant

economic burden for employers due to productivity loss[23,24]. For instance, after receiving epoetin alfa treatment, absenteeism in patients with CKD-related anemia had been reduced by 52.3 days, a 91.5% increase in productivity[25].

The healthcare costs for CKD patients increase with disease progression and the presence of their comorbidities[1,26]. Findings from the USRDS ADR 2016 illustrated that Medicare expenditure for CKD increased with CKD progression. Elderly patients with stage 4-5 had the highest per person per year Medicare spending in 2014, at $28,541, compared to $21,176 and $19,075 for patients with stage 3 and patients with stage 1-2. In addition, among patients with ESRD, per person per year Medicare spending reached $75,214, 3.3 times greater than overall CKD patients ($22,745)[1]. Thus, slowing the progression of CKD has substantial benefits on reducing financial burdens on the healthcare system. When considering the onset of comorbidities, the average expenditure per year at risk was highest in patients with all three chronic conditions of CKD, diabetes, and congestive heart failure ($38,561), followed by patients with comorbid CKD and congestive heart failure ($30,395), patients with comorbid CKD and diabetes ($18,610) and patients with only CKD ($15,673).

Given the larger number of comorbid conditions in CKD patients and the high cost of CKD-related treatments, substantial disparities in accessibility, utilization of CKD care and treatment outcome were observed across socioeconomic and racial groups[27,28]. On the one hand, health insurance plays an important role in increasing affordability of CKD care, improving CKD care quality and further improving treatment outcome. Among the CKD patients younger than 65 years in the United States, patients covered by private insurance were least likely to reach ESRD and die, compared to patients with public insurance and

uninsured[29]. There were more barriers to treatment among patients in developing nations than those in developed nations, because of the more expensive treatment and lack of insurance coverage[30]. On the other hand, population-based differences in treatment outcome may also be affected by patient's characteristics and healthcare quality. For example, the United States had a significantly higher incidence of ESRD than Europe counties, although comparable prevalence of CKD was observed[31]. An international comparison study by Hallan et al using nationally representative data illustrated CKD patients in the United States had a higher risk of progression from advanced CKD to ESRD than those in Norway. And this higher risk of progression in the United States might be attributable to late nephrologist referral and high rates of obesity and diabetes.

2.2 Renal function trajectory and CKD care

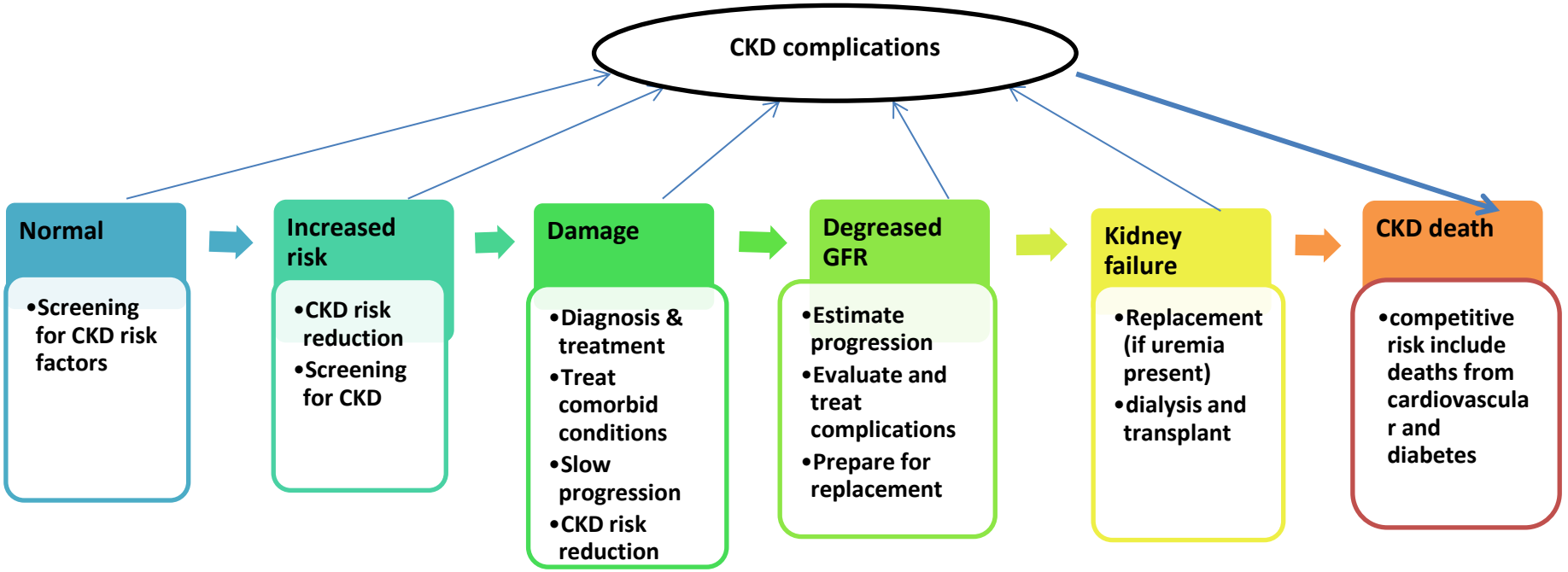
Humans are born with two kidneys, bean-shaped organs located in the upper abdominal area. Kidneys serve several essential roles in regulate the balance of body chemicals. The main functions of kidney include removing waste products of metabolism and regulating fluid balance through the urine system. By these actions that kidneys serve as the main pathway for drug excretion. The kidneys also produce a variety of important hormones, such as erythropoietin, calcitriol (1,25- dihydroxycholecalciferol) and renin . Erythropoietin plays a key role in regulating red blood cells production. Calcitriol, an active form of Vitamin D, can stimulate the small intestine for improving absorption of Ca2+ and phosphates, which are essential elements for bone growth and bone health. As a critical part of the renin – angiotensin–aldosterone system (RAAS), renin is able to regulate blood pressure.

Renal function declines with age, even among healthy adults. Loss of kidney function is varies substantially between population, and the decline rate usually follows a non-linear pattern[32]. Figure 2-2 illustrated an overview of the renal function trajectory and the corresponding healthcare services patients received[20,33]. In general, elderly adults who have diabetes, hypertension, cardiovascular disease or any family history of CKD are under higher risk of developing CKD. Patients with these diseases are more likely to be given screening tests for CKD, which include urine test for albuminuria and blood test for creatinine. Meanwhile, patients with diabetes or hypertension are recommended to control their blood pressure and glycemia to prevent kidney disease. When patients are diagnosed with CKD and the stage is confirmed, treatments are given to delay CKD progression and reduce CKD complications. If patients are diagnosed with early-stage CKD (stage 1-3), they will receive treatments for their comorbid conditions, which may include hypertension, diabetes and lipid control. On the other hand, if patients have advanced kidney damage and experience a steep decrease in GFR, they are likely to need kidney replacement in the near future. In that case, physicians will estimate progression, provide care for CKD complications, and prepare for kidney transplant. When kidney failure happens, patients need regular dialysis to remain alive until a new kidney is available for transplantation.

The decline in renal function may follow distinctly different patterns from patient to patient. Modifying treatment strategies based on the latest tests results and onset of comorbid conditions are preferred. Given these facts, CKD patients are recommended to monitor their kidney function by having physician order urine and blood tests at least once per year. More frequent monitoring is recommended by Kidney Disease Outcomes Quality Initiative (K/DOQI) for patients with advanced CKD[20]. Delaying the progression of CKD is a critical goal in CKD management, and it is also where oral medications can come into play.

Pharmacological therapies for CKD are the focus of our research, but before describing our study we will briefly introduce some important component of CKD care, as well as the comorbidities and complications of CKD.

Figure 2-2 Kidney function trajectory and corresponding care



Adapted from KDOQI guidelines

2.2.1 CKD screening, diagnosis, and staging

Early detection of CKD allows clinicians to provide medical interventions at an early stage, nevertheless, the awareness of CKD is extremely low as only 3%, 5%, 8% and 44% of CKD patients in stage 1,2,3, and 4 were aware of their kidney disease[1]. Therefore, implementing CKD screening programs is warranted. These programs can bring significant benefits to CKD patients in delaying the onset of ESRD, preventing the development of CKD complications, as well as reducing the risk of death from cardiovascular diseases[34]. Although approximately 13% of Americans are living with CKD, it is not uncontroversial to screen the general population without any selection. The consequences of "false positive" of laboratory tests induce unnecessary referrals, costs, and anxiety[35]. K/DOQI recommends screening people who have higher risk of developing CKD: elderly adults who have been diagnosed with diabetes, hypertension, cardiovascular disease, or having any family history of hypertension, diabetes or CKD. A study of NHANES participants aged 20-59 found the prevalence of CKD in adults with diabetes was 4 times greater than those without diabetes (33.8% vs. 8.2%). Meanwhile, CKD prevalence in adults with hypertension was 2.6 times greater than those without (18.9% vs. 7.4%)[36]. A study by Vassalotti et al. evaluated the Early Evaluation Program (KEEP) and found more CKD patients has been detected at early stage by targeting on high risk population, compared with the CKD prevalence estimated from NHANES data[37].

Procedures of CKD screening and diagnosis include several laboratory tests such as creatinine blood test, creatinine clearance test, blood urea nitrogen (BUN) test, and albumin urine test. GFR is an ideal indicator of kidney function, however, measuring GFR directly involves high cost and time-consuming. Instead, the 24-hour creatinine clearance and serum creatinine concentration have been measured to assess GFR. Considering the fact that kidney function varies across age, gender and race, several prediction equations have been developed

to calculate estimated GFR. The modification of diet in renal disease (MDRD) Study and Cockcroft-Gault equations have been widely used in adults, while the Schwartz and Counahan-Barratt equations have been applied in children.

In 2002, K/DOQI introduced the definition of CKD and classified its stages using laboratory measurements, regardless of underlying cause[20]. CKD had been categorized into five categories based on the estimated GFR and the presence of kidney damage. Table 2.1 lists these categories and their corresponding laboratory criteria. However, it is worth to note that using the threshold values from the K/DOQI guidelines alone to diagnose and classify CKD is dangerous. Physicians need to take age, race and gender specific reference values of estimated GFR into account, in order to make sound and reliable clinical judgments[38].

Table 2-1Definition and description of CKD stage

Stage	GFR	Description	ICD-9-CM code
I	≥ 90 mL/min/1.73 m^2	Kidney damage with normal or increased GFR	585.1
II	60–89 mL/min/ 1.73 m^2	Kidney damage with mild decreased GFR	585.2
III	30–59mL/min/1.73m^2	Moderately decreased GFR regardless of kidney damage	585.3
IV	15–29 mL/min/1.73m^2	Severely decreased GFR regardless of kidney damage	585.4
V and ESRD	<15mL/min/1.73m^2	Kidney failure regardless of kidney damage, or kidney failure treated by dialysis or transplantation (ESRD requires chronic kidney dialysis).	585.5 585.6
Adapted from the National Kidney Foundation's K/DOQI guidelines [20]			

2.2.2 Comorbid conditions of CKD

Hypertension

The study using national representative data indicated approximately 74% of CKD patients in the United States have hypertension as comorbidity[1]. Hypertension and CKD are related in two ways. On the one hand, hypertension is a major cause of CKD that uncontrolled high blood pressure damages blood vessels and consequently reduces the blood supply to kidney. The tiny filtering units in kidneys are also damaged by high blood pressure. On the other hand, hypertension is a common complication of CKD that reduced kidney function may lose their ability to remove extra fluid and regulate blood pressure. Thus, the rate of loss in kidney function is more likely to be accelerated by hypertension. A report of national health statistics illustrated hypertension is the second most common causes of ESRD after diabetes in the United States[39].

Hypertension is generally an asymptomatic condition. A recent national representative study found 29% of American adults had hypertension in 2011-2012, while 17% of them were unware of their high blood pressure[40]. Additionally, only 76% of hypertension patients took anti-hypertensive agents during the study period, and approximately half of them control their blood pressure under controlled. Given the facts that CKD patients with comorbid hypertension have relatively high medication burden and poor treatment outcome, our study will specifically focus on this vulnerable population, and examine their medication use patterns, as well as medication adherence outcomes.

Diabetes

Diabetes is the leading cause of kidney disease, which can harm kidneys in several ways: narrowing the blood vessels inside kidneys; damaging nerves in the bladder which may cause patients unaware of a full bladder, and further lead to an increased pressure of bladder; increasing risk of urinary tract infection caused by bacteria that reproduce rapidly in urine with a high sugar level[41]. Approximately 39% of American adults with CKD had diabetes as well[1]. Making blood pressure and blood glucose under controlled is recommended for patients with both diabetes and CKD. ACEIs and ARBs are recommended as first line therapy for this population, regardless the onset of high blood pressure[42].

2.2.3 CKD complications

Decline in renal function is associated with several serious complications, including anemia, mineral and bone disorders, and cardiovascular disease[43]. CKD complications are more likely to occur in patients with moderate or severe loss of renal function.

Anemia

As we discussed in the previous section, kidneys play an important role in a number of essential hormones to keep body healthy. Erythropoietin, the hormone produced by kidney, is an essential component of red blood cell production. Anemia happens when the human body is short of red blood cells, which provide energy for daily activities. Fatigue, feeling short of breath and sleep disorders are common symptoms of anemia[44]. Therapies including erythropoiesis stimulating agents and iron are recommended to improve energy and physical function for anemia patients with kidney dysfunction[45]. A recent nationally representative

study found 14% of American adults with CKD had anemia in 2007-2010, meanwhile the prevalence of anemia increased with the decline of kidney function[46]. The same study also found approximately only 23% of CKD patients with anemia received treatment, though anemia patients with moderate and severe kidney damage were more likely to receive treatment compared to those with mild kidney damage.

Mineral and bone disorders

Chronic kidney disease–mineral bone disorder (CKD-MBD) may present when kidney dysfunction causes an imbalance of calcium and phosphorus in blood[47]. Damaged kidneys cannot remove extra phosphorus from the body and convert Vitamin D to the activated form, calcitriol. A lower calcitriol concentration inhibits calcium absorption from food, and further reduces the level of blood calcium. Moreover, declined blood calcium stimulates the release of parathyroid, a hormone regulating calcium balance. Ultimately, a lower level of blood calcium, along with a higher level of blood phosphorus and parathyroid hormone cause calcium to be removed from bone to blood. Besides bone damages, high blood calcium and phosphorus levels will damage blood vessels and increase risk of cardiovascular disease as well. Common symptoms of mineral and bone disorders include bone pain, weak bones, and itchy skin. Lower phosphorus diet and therapies including phosphate binders, vitamin D and calcimimetics are recommended to patients with CKD-MBD[48]. Previous studies of Vitamin D deficiency in CKD patients found the prevalence rate of CKD-MBD varied from 55% to 83% from study to study, depending on different definition of conditions and study population characteristics[49–51].

Cardiovascular disease

Cardiovascular disease (CVD) ranked in the first place of mortality in both the general population and patients with kidney failure. Cardiac function interacts closely with renal function. First, common risk factors such as hypertension and diabetes could cause both cardiovascular disease and CKD. According to the most recent USRDS ADR, 5.3% of elderly Medicare beneficiaries had presence of both diabetes and CKD, and the prevalence of having diabetes and CVD was 13% in 2014[1]. Second, CVD may occur when kidney dysfunction leads to onset of anemia, metabolic bone disease, inflammation, or dyslipidemia[43]. Research evidence indicated that CKD was an independent risk factor of developing CVD[52]. Third, cardiovascular diseases may worsen kidney function through multiple mechanisms, like haemodynamic abnormalities, neurohormonal activation, inflammatory activation and potential adverse effects of diuretics[53]. A high prevalence of ESRD was observed among hospitalized Medicare beneficiaries with cardiovascular disease after discharge[54].

2.2.4 CKD progression and mortality

According to the clinical practice guideline by K/DOQI, the progression of CKD is defined as a decline in estimated GFR of >5 ml/min/1.73 m^2 within one year, or >10 ml/min/1.73 m^2 within 5 years, or present of Microalbuminuria/ Macroalbuminuria. The decline of kidney function follows non-linear patterns[55]. As we discussed in the previous section, CKD comorbidities and complications can accelerate the progression to kidney failure. For example, a study of CKD progression demonstrated that the progression rate is higher in patients with diabetes than non-diabetes, after controlling estimated GFR and albuminuria

levels[19]. Moreover, a numbers of CKD patients die from cardiovascular disease before presence of kidney failure[56].

CKD patients are at high risk of hospitalization and all-cause mortality, and the risk increased with disease severity. For example, in 2013, the all-cause hospitalization rate of Medicare beneficiaries with CKD was 2.5 times higher than their age-gender-race matched counterparts without CKD, at 627 hospitalizations versus 248 hospitalizations per 1,000 patient years at risk. Similarly, the all-cause mortality rates were 118 deaths and 48 deaths per 1,000 person years at risk among patients with CKD and without CKD. Also worthy of mention, a gradually decline was observed in both all-cause hospitalization rate and mortality rate among Medicare beneficiaries with CKD in the past decade[1].

2.3 CKD treatment and management

Treatment strategies for CKD are varied based on the underlying cause of kidney disease, onset of CKD comorbidities and complications. Oral medication therapy serves as a critical part of CKD therapy to control CKD complications and delay CKD progression. The purpose of our study is to assess the association between ACEI/ARB use and CKD outcomes in hypertensive CKD patients. Moreover, this study investigates not only ACEIs/ARBs, but also some other commonly used cardiovascular agents. A total of six types of cardiovascular agents are investigated: renin-angiotensin-system inhibitors (ACEIs and ARBs), other antihypertension agents (diuretics, calcium channel blockers, beta-blockers and calcium channel blockers) and lipid lowering agents (statins). The mechanisms of these cardiovascular agents are distinctly different. We will briefly introduce each of these drug classes in this section.

Renin-angiotensin-system (RAS) Inhibitors

ACEIs and ARBs are the two main drug classes under RAS inhibitors, which demonstrate renoprotective effects on kidney function in two ways: reducing blood pressure and reducing proteinuria[42]. RAS inhibitors play an essential role in regulating blood pressure[57]. Rein, released by kidney can convert angiotensinogen to angiotensin I. Angiotensin I can be further transformed to angiotensin II by enzymes including angiotensin-converting enzyme (ACE), chymase and other enzymes. Ultimately, angiotensin II controls blood pressure by stimulating angiotensin type 1 receptor (AT_1R) for vasoconstriction, and stimulating angiotensin type 2 receptor (AT_2R) for vasodilation and sodium excretion[58,59]. ACEIs and ARBs reduce blood pressure by blocking the pathway of RAS at difference places. ARBs directly blocked the stimulation of AT_1R, while ACEIs inhibit the activity of angiotensin-converting enzyme (ACE) and consequently reduce the level of angiotensin II. Besides the effect of lowering blood pressure, ACEIs and ARBs have substantial effect on reducing proteinuria. Proteinuria, when present, may be a consequence of impairments of glomerular permeability which is caused by increased glomerular capillary pressure. ACIEs and ARBs reduce proteinuria by maintaining the glomerular filtration barrier to proteins and reducing filtered protein-dependent inflammatory signals.

Common ACEIs agents include benazepril, lisinopril, ramipril, captopril, enalapril. Side effect of ACEIs include, but are not limited to, cough, low blood pressure, dizziness, headache, and increased uric acid levels. It is worth noting here the existence of serious but rare side effects of ACEIs, like kidney failure, liver failure, and allergic reactions. Common

ARBs agents include candesartan, eprosartan, irbesartan, losartan, olmesartan, and valsartan. Side effects of ARBs are similar with ACEI, but patients are more likely to tolerate ARBs.

Diuretics

Diuretics are used to control extracellular fluid volume expansion, which is established to be associated with hypertension. Thus, diuretics reduce blood pressure by excreting extra sodium and water out of the body. There are three types of diuretics, and each works by diverse means. Loop diuretics inhibit reabsorption of sodium in the thick ascending loop of Henle in the kidneys. Thiazide diuretics inhibit reabsorption of sodium in the distal convoluted tubule in the kidneys. Potassium-sparing diuretics can inhibit potassium-sparing exchangers in the distal convoluted tubule in the kidneys, aldosterone action, or epithelial sodium channels. Diuretics are commonly prescribed together with other antihypertension agents due to its mechanism of lowering blood pressure[42]. For example, the combination therapy of diuretics and ACEIs/ARBs performs better than monotherapy of ACEIs/ ARBs. This may because impair sodium reabsorption due to kidney dysfunctions stimulate release of renin from kidney, and further increase the level of angiotensin I. Moreover, adding diuretics to other anti-hypertension agents with side effect of sodium and water retention can help patients to get their blood pressure better controlled. Common loop diuretics include, but are not limited to, furosemide, bumetanide, and ethacrynic acid. Bendroflumethiazide and hydrochlorothiazide are examples of thiazide diuretics. Potassium-sparing diuretics include triamterene, spironolactone, amiloride, and so on.. Common side effects of diuretics include hyponatremia, dizziness and headaches.

Beta-blockers

Beta-blockers decrease the blood pressure by blocking adrenergic receptors, primarily beta-1 receptors in the heart, and further dropping heart rate. Meanwhile, beta-blockers are able to work on beta-2 receptors located in blood vessels, which dilate blood vessels and consequently reduce blood pressure. Beta-blockers that are available for use include atenolol, metoprolol, propranolol, bisoprolol, and timolol. Beta-blocker may cause diarrhea, stomach cramps, nausea, and vomiting. Additional cautions are needed for patients with heart disease, because beta-blockers may cause heart failure in these populations.

Calcium channel blockers

Calcium channel blockers reduce blood pressure by dilating the arteries, and further reducing the pressure in arteries. There are two types of calcium channel blockers: dihydropyridine (DHP) calcium channel blockers (e.g. felodipine, isradipine, and nifedipine) and non-dihydropyridine (e.g. diltiazem and erapamil). The side effects of calcium channel blockers include headache, constipation, rapid/slow heart rate, and so on.

Statins

Statins are one of main types of lipid lowering agents, which can reduce the levels of cholesterol in blood by blocking the pathway of producing cholesterol in the liver. Although statins are not blood pressure lowing agents, but they play an important role in keeping vascular health, and preventing presence of cardiovascular diseases. Statins that approved for use include atorvastatin, cerivastatin, fluvastatin, lovastatin and so on. Side effects of statins include, but are not limited to, headache, difficulty sleeping, muscle aches.

2.4 Medicare prescription drug plans

Numerous studies have investigated the positive impact of health insurance on access to medication and medication adherence[60–62]. The subjects of our study are elderly Medicare beneficiaries with prescription drug coverage. In this section, we will briefly introduce the Medicare program, particularly focusing on the Medicare prescription drug plans.

Medicare is a national social insurance program, which aims to provide health insurance for Americans aged 65 or older beginning in 1966. Medicare has expended its coverage to younger adults with disabilities and people with ESRD since 1972[63]. There are four components under Medicare. Part A is hospital insurance which covers hospital care, skilled nursing facility care, nursing home care, hospice and home health service. Part B is medical insurance which covers outpatient services or supplies that are not covered in Part A. Services like preventive care, ambulance services, and durable medical equipment are covered in Part B. Part C plans are also called Medicare Advantage Plans (MA), which are alternative choices of Part A and Part B, launched in 1997. Different with original "fee-for-service" Part A and Part B, Part C plans are capitated-fee health plans. Moreover, Part C plans generally provide additional benefits to their beneficiaries including dental and prescription drug coverage. Over the past decade, the enrollment rate of Part C increased from 16% to 31% (2006-2015)[64]. Part D was introduced in 2006 to provide prescription drug benefits. Medicare beneficiaries who enrolled both Part A and Part B are eligible for Part D. Enrolling in Part D plans is optional, but a late enrollment penalty will be charged to people who do not enroll Part D when fist eligible for Medicare. Part D enrollment rate has increased over time since its implementation.

Overall, Medicare beneficiaries can get prescription drug coverage from either a stand-alone Prescription Drug Plans (PDP) or a Medicare Advantage plan included prescription drug coverage (MA-PD). In 2015, approximately 45% of Medicare beneficiaries receive prescription benefits from standalone PDP, while 24% of them receive the coverage from MA-PD. Part D plan designs are required to meet the feature of "standard benefit plan" defined by the Centers for Medicare & Medicaid Services (CMS) annually. The list of covered drugs, also called formulary, varies between Part D plans, and so do cost-sharing and utilization requirements. Prescription drugs for common chronic conditions like anti-hypertension agents, anti-diabetes agents and antihyperlipidemic agents are covered. Besides the monthly premiums, beneficiaries need to pay 100% of their prescription costs until the initial deductible is met ($360 in 2016). Then beneficiaries pay 25% of drugs costs before the total costs reaching the initial coverage limit ($3310 in 2016). After that, beneficiaries fall into a coverage gap, also called donut hole, which is designed to control overuse and inappropriate use of medication. During this time period, beneficiaries have to pay 100% of their drug costs up to the out-of-pocket threshold ($4,850 in 2016), although they may receive certain discounts on the brand-name drugs and generic drugs (55% and 42% in 2016). The Affordable Care Act (ACA) is gradually closing this coverage gap and will eliminate it by 2020. Once beneficiaries getting out of donut hole, they are eligible to receive catastrophic coverage benefit, where only a fixed amount or 5% of the retail price will be charged.

There is an extra Help program, also known as the Low-Income Subsidy (LIS) under Medicare Part D[65]. The LIS provides subsidies for the monthly premiums, deductibles and copayments to help low income beneficiaries pay their prescription drugs. Some Part D enrollees are automatically qualify for the LIS ("deemed LIS beneficiaries), those includes

beneficiaries who are dually eligible for both Medicare and Medicaid, who are Supplemental Security Income (SSI) recipients, and who are enrolled in the Medicare Saving Programs (MSP). The rest Part D beneficiaries need to apply for the LIS ("non-deemed LIS beneficiaries) and their eligibilities are determined by the State Medicaid office or the Social Security Administration (SSA).

According to the 2016 USRDS ADR, comparable Part D enrollment rate was observed in Medicare beneficiaries with and without CKD (71% vs 66%). However, elderly adults with CKD carried a higher overall drug burden compared with those without, as total prescription spending for Part D enrollees with CKD was 50% higher than general Part D enrollees ($4,198 vs. $2,806 per person per year). Additionally, LIS program improves access and affordability of needed medications in the most vulnerable population. The 2016 USRDS ADR reported total prescription spending for CKD patients with LIS was more than 2 times greater than those without LIS, at $7,352 compared to $3,262. Moreover, out-of-pocket cost accounted for only 1% of total prescription spending in LIS population while accounted for 29% in non-LIS population.

2.5 Neighborhood and population health

Geographic variation exists in health risks, utilization of healthcare services and health outcomes. Characteristics of residential neighborhood, like neighborhood social support, social economic positions, primary care resources and health care quality may account for these geographical differences in health behaviors, disparities in healthcare utilization and outcomes. People living in the same area are more likely than those from different areas to have similar lifestyle, health-related beliefs, health behaviors and healthcare system. Thus, by

targeting contextual characteristics, population-based strategies can yield greater public health impact on health promotion, from a population perspective. Here we discuss some important neighborhood characteristics related with health improvement.

Neighborhood support and participation

Social support and social participation at neighborhood level are showed to have positive effects on population health. A study of neighborhood support and infant's birth weight in Chicago revealed that the difference in birth weight between African-American and White was reduced from 297g to 154g by adjusting for individual factors, and was further reduced to 124g by adding adjustment of neighborhood social support[66]. Another study investigated the effect of neighborhood on medication use in women aged above 45 found residents with low social participation were less likely to use hormone replacement therapy compared to their counterparts with active social participation[67]. Residents might benefit from neighborhood support and participation from sharing health promotion information, adopting healthy norms of behaviors, and promoting perceived psychological well being[68–71].

Neighborhood socioeconomic status

Research evidence indicates the effect of residing in a deprived neighborhood on risk behaviors, presence of diseases and poor treatment outcomes persists, even after adjusting for individual socioeconomic status. For example, a multilevel study on the relationship between neighborhood and drug use revealed living in poverty neighborhoods increased the risk of using heroin and cocaine, after adjusting individual factors[72]. Previous studies also found people living in deprived areas were more likely to have hypertension, obesity, and developing cardiovascular disease[73]. Also, treatment outcome is relatively poor in deprived

areas. Shacham et al examined the relationship between neighborhood characteristics and HIV managements in outpatient settings in the St Louis metropolitan area[74]. Researchers found people from deprived areas were less likely to receive antiretroviral prescription and demonstrated a lower CD4 count. A cohort study in patients after discharge for acute myocardial infarction (AMI) conducted by Tonne et al demonstrated that people living in affluent census tracts had a significant higher survival rate compared with those living in poor census tracts, with adjustments for individual, clinical and socioeconomic factors[75].

Health care resources

Variation in health resources across regions also accounts for disparities in utilization of health care and population health. Research evidence from ecological studies illustrated that better access to primary care, measured by number of primary care physicians per capita, was associated with less hospitalizations and a lower mortality rate[76–78]. Findings from these studies indicated that improving access to primary care might reduce disparities in mortality between socioeconomic and racial/ethnic groups. Furthermore, previous study found a positive relationship between physician-population-ratio and adherence to practice guidelines in the fibromyalgia setting[79]. Patients in the area with higher physician density were less likely to have chronic opioid use, a treatment with insufficient evidence for therapeutic efficacy, compared with those in the medically underserved area. The increased adherence to the practice guidelines might be attributable to more information dissemination between physicians, increased awareness of the guideline and familiarity with the guideline as results of less work burden.

Treatment strategies and healthcare quality

Disparities in population health may also be due to distinct treatment strategies and healthcare quality between regions. Two studies of medication use in Medicaid enrollees showed there were significant differences in both opiates use and antiretroviral agents use across the United States[80,81]. This difference might be raised by the distinct design of state Medicaid programs and different medical practice between physicians. A recent study by Sargen et al assessed diabetic drugs use in Medicare enrollees across hospital referral regions[82]. Findings from this study indicated metformin and thiazolidinedione were more likely to be prescribed to people in the Western United States and the Central United States respectively, while sulfonylureas and insulins were both widely used in the South and Midwest. Race and income were associated with prescription patterns as well.

With regards to the quality of healthcare, two studies from England examined how healthcare quality varied across regions, and illustrated that the quality of health services, like preventive care, was better in regions with higher social economic positions[83,84]. Meanwhile, more programs were available for chronic diseases, like diabetes and asthma, in affluent regions than deprived regions. When specific to medication use, a study of high risk medications use in Part D enrollees found people residing in the Southern United States were more likely to receive the pharmacological therapy including high risk medications, compared to their counterparts living in the New England area[85].

2.6 Cardiovascular medication use among patients with hypertensive CKD

2.6.1 Patterns of cardiovascular medication use

CKD patients are at high risk of uncontrolled blood pressure and cardiovascular conditions. Approximately two thirds of American adults with CKD had inadequate blood pressure control[86]. For this reason, cardiovascular medications are the most frequently used therapeutic groups in people with CKD not requiring dialysis. Combination therapy with two or more drugs is necessary when the target blood pressure cannot be achieved by using a single drug. Therefore, CKD patients were taken more anti-hypertension agents than their hypertensive counterparts[4,87,88]. A cross-sectional study of 13,065 REGARDS (Reasons for Geographic and Racial Differences in Stroke) participants showed that the prevalence of receiving 4 and more types of antihypertensive agents in CKD participants was 2 times greater than those without CKD (10% vs.5%)[88]. Despite a majority of both participants with and without CKD receiving two antihypertensive agents (37% and 40%), participants with CKD were more likely to receive three different antihypertensive agents (27% vs.17%) and less likely to receive a single drug, compared to those without CKD (26% vs. 39%).

Patterns of cardiovascular agents use are individualized based on therapeutic goal, efficacy, tolerability, complexity of regimen, and cost. There is little research describing the patterns of cardiovascular agents use in CKD patients[89–91]. Bailie et al (2005) used data from the RRI-CKD study (the Renal Research Institute Chronic Kidney Disease study) found CKD patients were most likely on calcium channel blocker (52%), followed by beta-blocker (46%), ACIEs (44%), Statins (16%) and ARBs (13%)[92]. Furthermore, medication use was varied by co-existing conditions. For instance, CKD patients with proteinuria and diabetes demonstrated the highest utilization rate of calcium channel blocker (64%), while CKD

patients with coronary artery disease had the highest utilization rate of beta-blocker (65%) and statins (24%). A noticeable higher utilization rate of ACEIs was observed in both proteinuric patients with and without diabetes (58% and 52%), while a higher utilization rate of ARBs was only showed in proteinuric patients without diabetes (23%). Another study examined 420 pre-dialysis CKD patients and found a relatively high utilization rate in all cardiovascular agents. Diuretic ranked first in term of utilization rate (80%), followed by RAS inhibitors (67.1%), calcium channel blocker (64.8%), beta-blockers (42.4%), and statins (36.2%). Different with other studies, this study collected medication use data during the period from the first nephrology consultation to initiation of dialysis. Thus, the high utilization rate in this study population may attributable to having advanced CKD and seen by nephrologists[89].

Factors that associated with cardiovascular agents use in CKD patients are not well studied. A recent national representative study of NHANES participants explored factors associated anti-hypertensive agents use in CKD patients[91]. In this study, CKD patients who were older, aware of hypertension or diabetes, and had advanced kidney damage were more likely to take anti-hypertensive agents. Additionally, significant differences in utilization rate by CKD stages were only observed in ACEIs and diuretics, but not in ARBs, beta-blockers and calcium channel blockers. Another study in New Mexico HMO (health maintenance organization) enrollees found diabetic CKD patients showed a higher utilization rate of ACEIs than those without diabetes regardless of disease severity[93]. There was no noticeable difference in ACEIs use between patients with and without a nephrology referral.

2.6.2 Outcome associated with cardiovascular medication use

This section describes the existing evidence on the efficacy of each cardiovascular agent in the CKD population. Although all antihypertensive agents are effective in lowering blood pressure, some drug classes might bring additional benefits besides lowering blood pressure when they are used to treat some specific types of CVD and CKD[42].

ACEIs/ARBs

According to the K/DOQI clinical practice guidelines, regimens including ACEIs and ARBs are preferred for diabetic nephropathy and nondiabetic nephropathy with level of proteinuria greater than 200 mg/g[42]. The American College of Physicians (ACP) also recommends use of ACEIs and ARBs to patients with hypertensive CKD[94]. The Irbesartan Diabetic Nephropathy Trial (IDNT) compared the protective effect of ARBs and calcium channel blockers in hypertensive patients with kidney disease due to type 2 diabetes[95]. A total of 1,715 patients were randomly assigned to treatment with irbesartan, amlodipine or placebo. Compared to the other two groups, patients received ARBs demonstrated a significantly slower increase in the serum creatinine concentration, a lower risk of doubling the serum creatinine concentration and less likely to develop ESRD. However, there was no difference in term of all case mortality and cardiovascular related outcomes. Another randomized controlled trial (RCT) study of 352 patients with nondiabetic kidney disease found patients receiving regimens including the ACEI ramipril showed a slower decline in GRF and a reduced proteinuria, compared with patients receiving conventional antihypertensive regimens[96]. Furthermore, the protective effect of ACEI treatment was independent of changes in blood pressure. Findings from these studies indicate ACEIs and ARBs have renoprotective effects in addition to lowering blood pressure.

Diuretics

Diuretics are preferred antihypertensive agents for heart failure with systolic dysfunction, reducing risk of recurrent stroke and coronary artery disease[42]. A RCT study of 4,336 elderly patients with isolated systolic hypertension and kidney disease showed patients receiving therapies including diuretic were less likely to experience adverse cardiovascular events within a 5-year observation period[97]. Meanwhile, research evidence indicated that adding diuretics to regimens with ACEIs/ARBs may strengthen the efficacy of antihypertensive treatments[42]. A pilot RCT study from Weir et al assessed effect of the ARB valsartan on blood pressure in hypertensive African Americans who were on low salt diet[98]. A total of 88 patients on a 100 mEq Na+/day diet received valsartan therapy (160 mg/day) for 4 weeks at first, then they received the same valsartan therapy with a supplementation of 100 mEq Na+/day for another 4 weeks. After that, patients were randomly assigned three different regiments while continuing the high salt diet for additional 6 weeks: doubling the dose of valsartan, adding the diuretic hydrochlorothiazide (12.5 mg/day) or the ACEI benazepril (20 mg/day) to the baseline valsartan therapy. This study found the effect of valsartan on lowering blood pressure was not significantly diminished by high salt diet. Moreover, combination therapy of an ARB and a diuretic was more effective in lowering blood pressure than the therapy either adding an ACEI or doubling the dose of ARB.

Beta-blockers

Beta-blockers are of particular benefits in patients with angina, myocardial infarction, and congestive heart failure and so on.[42]. The cardiac insufficiency bisoprolol study II (CIBIS-II) trial demonstrated that patients with heart failure and kidney dysfunction who received the beta-blocker bisoprolol had a lower risk of all-cause mortality and heart failure hospitalization than comparison group, and these protective effects were observed in all

patients regardless the severity of renal impairment at baseline[99]. Similarity, findings from the Seniors with Heart Failure (SENIORS) trial and the Metoprolol Controlled-Release Randomised Intervention Trial in Heart Failure (MERIT-HF) trial showed that the benefits of beta-blockers in reducing risk of hospitalization and modality were comparable between patients with mild and moderate kidney insufficiency[100,101].

Calcium channel blockers

Calcium channel blockers are recommended for some specific types of CVD, such as congestive heart failure due to diastolic dysfunction and angina pectoris[42]. Besides the effect of regulating blood pressure, there is strong evidence that nondihydropyridine calcium channel blockers have added benefits of slowing the progression of diabetic kidney disease by reducing proteinuria. A RCT study of 34 Africa American patients with hypertension and diabetic kidney disease found patients who received the calcium channel blocker verapamil had a slower decline of creatinine clearance and a greater reduction in proteinuria compared to those received the beta-blocker atenolol, despite comparable blood pressure control[102]. Another RCT study of 92 normotensive patients with insulin-dependent diabetes and microalbuminuria found treatment group with the calcium channel blocker nifedipine demonstrated a marked lower risk of progression to clinical albuminuria and macroalbuminuria compared to placebo group over a 3-year study period[103].

Statins

Use of statins in hypertensive CKD is recommended in the clinical practice guideline from ACP[94]. As reported in the USRDS ADR 2016, statins are the most commonly used oral

medication in CKD patients regardless the stage and cause of kidney disease[1]. Previous studies have revealed the cardiovascular benefits of statins in CKD patients, nevertheless there was lack of RCT evidence for benefits in preserving kidney function[104–106]. A meta-analysis study by Navaneethan et al included a total of 26 RCTs and quasi-RCTs and found non-dialysis dependent CKD patients who received statins had a significant lower risk of cardiovascular mortality and all-cause mortality compared to those received placebo or regimens without statins[107]. In term of kidney function, there was no difference in creatinine clearance between statins and non-statins groups, but a greater reduction in 24 hour urinary protein excretion was observed in statins group.

2.6.3 Adherence to cardiovascular medications in CKD patients

Medication compliance is the cornerstone in achieving the goals of pharmacological treatments[108]. A number of studies revealed that poor adherence to prescribed medication was associated with increased hospital admissions and mortality[109–112]. Consequences of poor medication-taking behaviors accounted for more than $100 billion in healthcare expenditures per year[113,114]. CKD patients are at high risk of poor medication adherence due to presence of depression, development of functional and cognitive impairment, complex medicine regimens and pill burden[115–119]. Previous studies found hypertensive CKD patients who had poor adherence to their prescribed medications were less like to make their blood under controlled and consequently more likely to experiencing progression of CKD[4,88,120]. However, adherence to medications, especially adherence to cardiovascular agents, has not been extensively studies in patients with CKD not yet on dialysis.

A broad range of adherence rate ranging from 65% to 83% was observed in studies of medication adherence in CKD patients[4,88,120–123]. This variation may attributable to different study designs, type of the target medications and heterogeneity in study populations. There is no standard method to measure medication adherence, and accordingly definition of nonadherence are varied across studies[124]. Medication adherence can be assessed either directly or indirectly. Direct methods include testing the concentration of drug in blood or urine, measuring biomarkers with the investigated medications, and direct observation of taking medication[114]. Though direct methods reflect medication taking behaviors, seldom studies use indirect methods because they are costly and labor-intensive. Indirect methods of assessing adherence are frequently used in adherence studies, including patient self-reports, prescription records from electronic databases, medication monitoring in form of pill counts and using electronic monitoring devices.

In general, adherence studies with self-report measures showed better medication compliance from 67% to 83%[88,120,121] than those with objective measures from 65% to 70%[4,122,123]. This difference may be attributable to the recall bias and social desirability bias from self-reports. It is worthwhile to note that self-reports such as questionnaire and diary methods have moderate-to-high concordance with electronic measures, while interview-based self-reports have poor concordance[125]. Studies using self-report measures have advantage in obtaining subjective reasons for medication nonadherence and early discontinuation, such as health belief and perceived treatment effects[126]. Studies using prescription claims data have advantage in relatively large sample size, long observation period, timely and inexpensive compared to other measures. While worthy to note is that medication records reflects the total quantity of doses taken but not daily doses taken and timing of doses. Moreover, the accuracy of claims data is questionable when patients can obtain their prescriptions from other outside

resources, and when researchers cannot distinguish decisions of discontinuation made by physicians because of lack of efficacy and decisions made by patients because of poor adherence[127]. Pill counts and electronic monitoring devices are commonly used to monitor medication taking behaviors as well. Use of pill counts is simple and economic, but it is not accurate as the patients may discard pills before visits[128]. Use of electronic monitoring devices is relatively costly and may not be an ideal method for conditions needing multiple prescriptions. But this method has an additional advantage in capturing timing of dose taken and detecting drug holidays[129].

Reasons for nonadherence to prescribed medication vary by conditions, characteristics of the target medication and investigated populations. A meta-analysis conducted by DiMatteo reviewed a total of 568 adherence studies in all fields from 1948 to 1998, and found education, income and socioeconomic status were positively related with adherence to medical recommendations. However, the effects of age and gender on adherence were varied across studies[130]. Similarly, when examined medication adherence in CKD patients, younger age, male, lower levels of income and education were risk factors of poor adherence in some studies but not in others[88,120,121,131].

Medication adherence in CKD patients is also influenced by patients' health status. Previous studies found CKD patients who were unable to self-administer their medications, had presence of depression and had more hospital visits demonstrated a lower adherence rate to their medications[4,88,121]. Inconsistent evidence was observed from study to study regarding to the association between kidney function and adherence. Schmitt et al using pharmacy claims found patients with worse kidney function had a lower medication adherence; while a study

of the African American Study of Kidney Disease (AASK) participants using self-reported adherence measures found CKD patients with moderate and severe CKD were more likely to be adherent to their medications than patients with mild CKD[4,131]. A retrospective cohort study by Chang et al found medication adherence was associated with worsening kidney function at baseline in use of ACEIs and beta-blockers, but not in use of statins[123].

Forgetfulness was the most common reason for unintentional nonadherence given by patients[88,120,132]. Besides that, research evidence revealed that medication taking behaviors were also related with characteristics of regimens, such as complexity of medicine regimens, pill burden, the salience of conditions, perceived need of medications, perceived benefits of medications, side effects and effective physician-patient communications[121,132–134]. Normally, CKD patients have a higher pill burden compared to the general population. A prospective cohort study showed CKD patients took an average of 6.7 pills per day[121]. Moreover, CKD patients may receive their prescribed medications not only from nephrologists but also from other physicians depending on their existing comorbid conditions. This makes the regimens more complex for CKD patients. Recent interview-based studies found that CKD patients prioritized their prescribed medications and skipped the medications perceived as less important[133,134]. For example, statins, medications for an typically asymptomatic disease dyslipidaemia, were often underutilized in both elderly population and CKD patients[135,136]. This might because lipid lowering agents were perceived as less important in preserving kidney function[133,134]. A qualitative study by Tolmie et al found that low adherence to lipid lowering agents were related with patients' understanding about cholesterol and lipid lowering agents[137].

Previous studies have assessed the treatment effect of medication adherence in hypertensive CKD patients. Hong et al used data from the AASK trial study and found poor adherence increased the visit-to-visit variability of systolic blood pressure. In this study, a total of 988 AASK participants were followed by one year and medication adherence was measured by self-reports and pill counts[131]. Another adherence study of 7,227 CKD patients using two year claims data showed patients who had poor adherence to their prescribed antihypertension were 23% more likely having uncontrolled blood pressure[4]. However, few studies had investigated the effects of medication adherence on the progression of kidney disease. Previous studies indicated that medication adherence declined over time. Two studies conducted by Magacho et al and Change et al found medication adherence rate in patients with kidney dysfunction decreased by 54% in a one-year period and 29% in a three-year period[121,123]. Thus, further studies with large sample size and examining long-term effects of medication adherence on renal function preservation are warranted.

As pointed out by the report of the World Health Organization, health professionals, not only general practitioners but also nurses, pharmacists, and psychologists play an essential role in promoting adherence to treatment[108]. Several review papers summarized the effectiveness of interventions aiming to improve medication compliance and treatment outcomes, and found the effects were inconsistent across studies[138–140]. Multidisciplinary care is also recommended in the CKD setting[141]. Research evidence indicated that interventions with either nurse coordinated care or pharmacist coordinated care increased use of cardiovascular medications and consequently reduced medication-dependent risk factors, like hypertension and cholesterol[142–145]. However, there is lack of evidence that these interventions can significantly reduce cardiovascular events and mortality. Though substantial studies have evaluated factors related with poor adherence in CKD patients, few of them focuse on factors that influence the

access to medications from perspective of neighborhood, characteristics of the place that patients lived in. Our study will illustrate how contextual factors impact medication adherence in CKD patients across different regions. The findings of our study will support health professionals in developing locally population-based interventions to improve medication taking behaviors and further promote treatment outcomes.

2.7 Conceptual Model

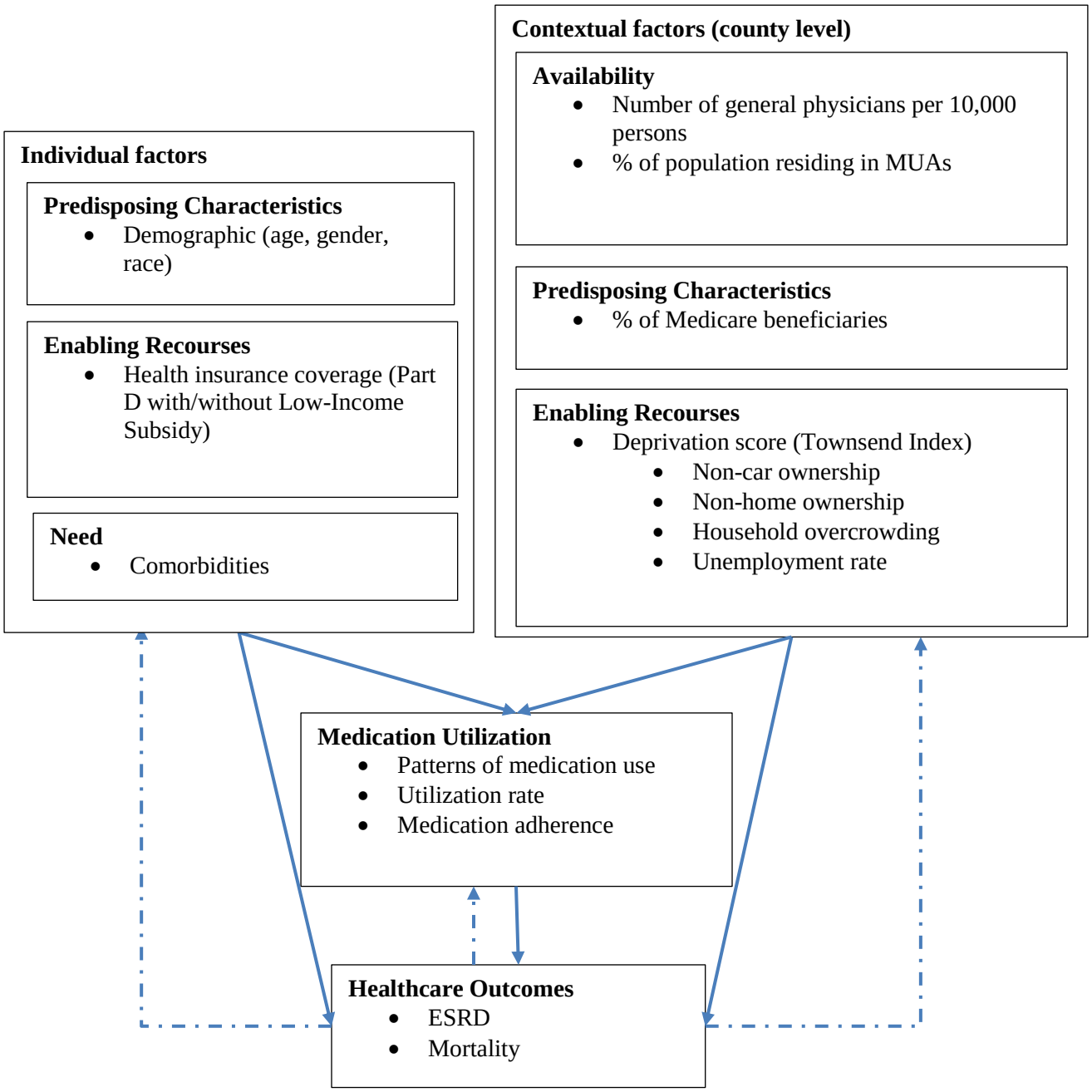
Health behaviors and health outcomes are jointly determined by characteristics of environment and population at risk. This forms the basis of Anderson's Behavioral Model, developed by Aday and Andersen, which has been widely used in health services research to predict healthcare utilization and outcomes over the past decades[146]. The conceptual framework of this study is developed based on Andersen's Behavioral Model (Figure 2-3). Three components of individual determinants of health behaviors and outcomes are proposed in Anderson's model, which are predisposing, enabling, and need. Predisposing refers to the properties exist prior to the onset of conditions. Demographic, social structure and health beliefs factors are generally viewed as predisposing characteristics. The enabling component describes individuals' potential accessibility to health care. The need component indicates disease severity, which can be captured by either patient-perceived severity or that evaluated by health professionals. We will conduct this study using health claims data, so we are lack of measures for the subjective concepts in Anderson's Behavioral model, such as individuals' health belief and perceived severity. Demographic factors including age, gender, and race are captured in our study. Access to care is measured by prescription drug coverage. Patients' comorbidities are indicators of need for care, which are captured by diagnosis in medical claims.

Furthermore, we also define three dimensions of contextual determinants of health behaviors and outcomes, including availability, predisposing characteristics and enabling resources. Availability describes the characteristics of health system, such as volume and distribution of medical resources in an area, as at the county level in this study, which are measured by number of general physicians per 10,000 persons and percentage of people residing in MUAs. Predisposing characteristics and enabling resources have the same meaning as at the

individual level. Therefore, census statistics of external environments will serve as proxies of these concepts. Percentage of Medicare beneficiaries indicates the predisposing characteristics in each county. Deprivation score is used to assess the enabling resources at country level, which is measured by the Townsend index. The Townsend index incorporates unemployment rate, percentage of households without car ownership, home ownership and overcrowding.

Healthcare utilization of interest in this study is ACEIs/ARBs use among elderly hypertensive patients with CKD, and the healthcare outcomes are defined as CKD related treatment outcomes. Based on our conceptual model, individual and contextual characteristics will directly affect healthcare outcomes or indirectly affect them through healthcare utilization. Our conceptual model will be useful to identify mutable variables that explain use of ACEIs/ARBs, and further promote equitable access via policies. Generally, variables under enabling components demonstrate a higher degree of mutability than other components[147].

Figure 2-3 Conceptual Model



Chapter 3

METHODOLOGY

This study assessed the relationship between access to cardiovascular medications, medication use, and CKD related outcomes among Medicare beneficiaries with hypertension and CKD in the United States. This section details the study design, study population, and measurements, as well as statistical methods implemented by each of the three study aims.

3.1 Study design

This was a retrospective cohort study of aged Medicare beneficiaries who had hypertension and CKD in the United States. We utilized the 5% sample of Medicare claims (from January 1, 2006 to December 31, 2013) data from the USRDS databases, Medicare claims data have been widely used in health services research for several reasons. First, elderly adults are at high risk for chronic kidney disease. Second, the 5% Medicare claims are nationally representative for Medicare beneficiaries who are not enrolled in a Medicare Advantage plan. The 5% sample of Medicare claims data contains claims from a 5% random sample of Medicare beneficiaries, whose CMS Health Insurance Claims number has the last two digits of 05, 20, 45, 70 or 95. Claims from hospice, inpatient hospitalizations, skilled nursing facility, outpatients, physician/supplier, home health agency, durable medical equipment, and prescription drug event are accessible. Third, since 2006, the year Medicare Part implemented, researchers are able to obtain medication use information from the Medicare

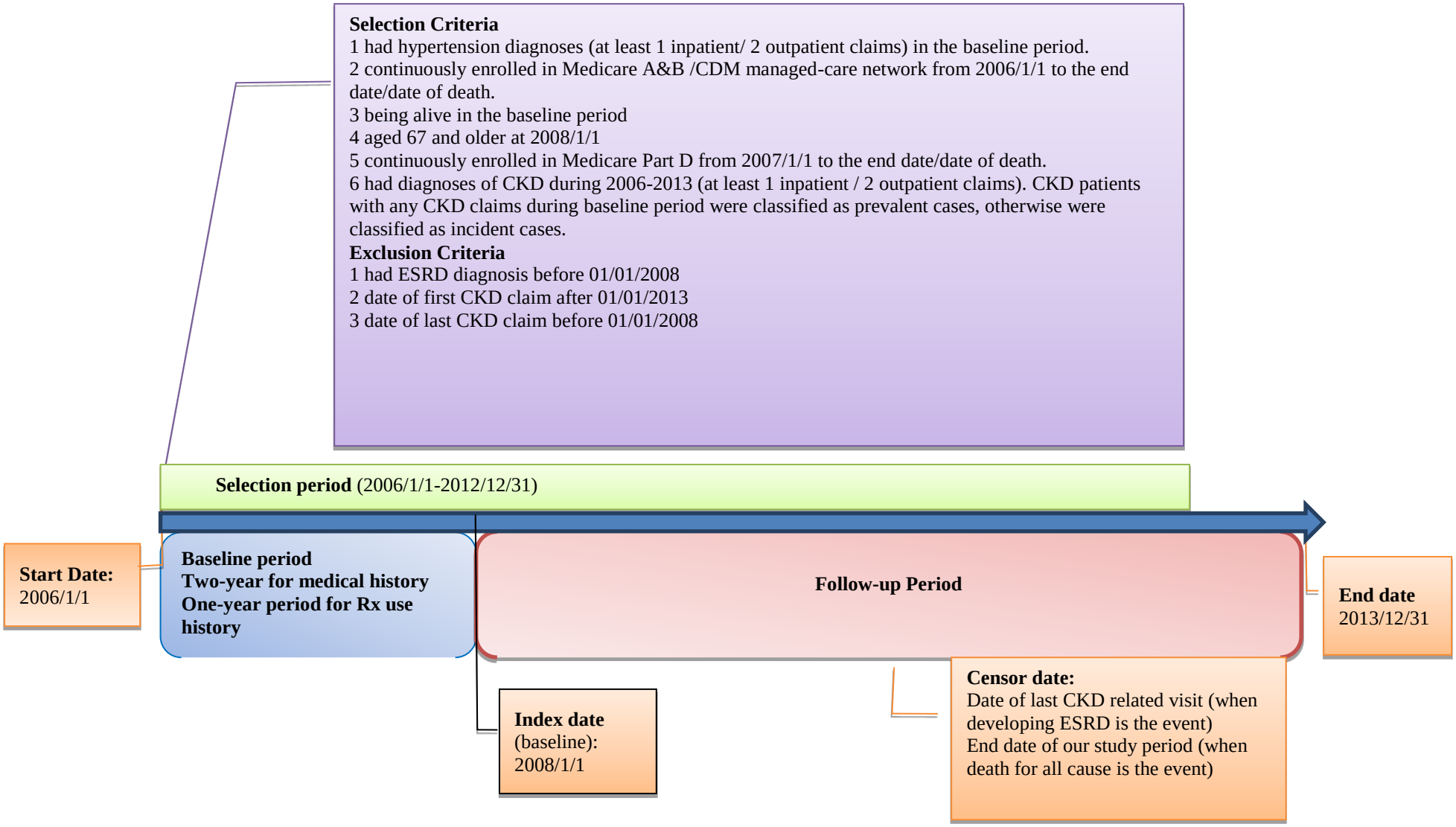
Part D claims data. ACEIs and ARBs, along with other cardiovascular agents are covered by all of Part D claims. Thus, as long as the patients filled their prescriptions from the Medicare Part D network, these are recorded in this electronic system. Moreover, the sampling design of Medicare 5% sample data also supports a longitudinal study design over years, which enable researchers to assess the long-term benefits of pharmacological treatment, such as CKD progression and mortality in CKD patients.

Figure 3-1 showed the overall study deign and study cohort extraction criteria. Our study comprised four main periods: a seven-year selection period (from 01/01/2006 to 12/31/2012) to select all hypertensive Medicare beneficiaries who had a diagnosis of CKD; a two-year baseline period (from 01/01/2006 to 12/31/2007) to assess medical history; an one-year look baseline period (from 01/01/2007 to 12/31/2007) to evaluate medication use history; and a six-year follow-up period (from the index date, 01/01/2008 to the end date, 12/31/2013) to examine long-term medication use and associated treatment outcomes. The primary outcomes in this study included medication use patterns, medication adherence, and progression to ESRD, as well as all-cause mortality. Patients were censored at the date of death or the date of last recognized CKD related visit when progression to ESRD was the event, while they were all censored at the end date of our study when all-cause mortality was the event.

In order to capture complete medication histories, continuously covered by Medicare stand-alone Part D plans from the beginning of 2007 to the end of 2013 were required. We identified the eligible hypertensive CKD patients starting from a retrospective cohort of hypertension patients, beneficiaries with diagnosis of hypertension in the two-year baseline period. We then included patients who had been diagnosed with CKD during the selection period. To ensure each eligible hypertensive CKD patients having a long enough follow-up

time, the selection period was ended one year ahead of the end date of this study. Beneficiaries whose first observed CKD claim was before the index date were classified as prevalent CKD, while the rest were classified as incident CKD. Subjects who developed ESRD or died in the two-year baseline period were excluded from our study. This study was approved by University of Michigan's Institutional Review Board (IRB).

Figure 3-1 Overall Study design and study cohort selection criteria



3.1.1 Data sources and linkage

The 5% sample of Medicare claims (2006-2013) from the USRDS databases were used in this study to obtain individual information on aged beneficiaries who enrolled in Part D. To achieve the study aims, these data sets were further linked to the U.S. Census Bureau American Community Survey (ACS) 5-Year Estimates data (2009-2013) for characteristics of external environmental status, and to the Health Resources and Services Administration (HRSA) Primary Care Service Area (PCSA) data (2007) for primary care resources in the county level. This unique dataset also contained spatial information of population center, obtained from Map of Centers of Population from the U.S. Census Bureau (2008)[148].

The 5% sample of Medicare claims from the USRDS databases consist of data from the CMS Medicare 5% Sample Standard Analytical Files (SAFs), ESRD related information extracted from the ESRD Medical Evidence form (CMS 2728), and death related information extracted from the ESRD Death Notification form (CMS 2746) as well as the Master Beneficiary Summary File. The CMS Medicare 5% Sample SAFs contains claims from a 5% random sample of Medicare beneficiaries. In the USRDS database, the unique Health Insurance Claim Number and Beneficiary Identification Code are used to match ESRD and death information to Medicare claims for beneficiaries in the 5% Medicare cohort. In this study, we used these linked datasets in the USRDS databases to identify our eligible study cohorts.

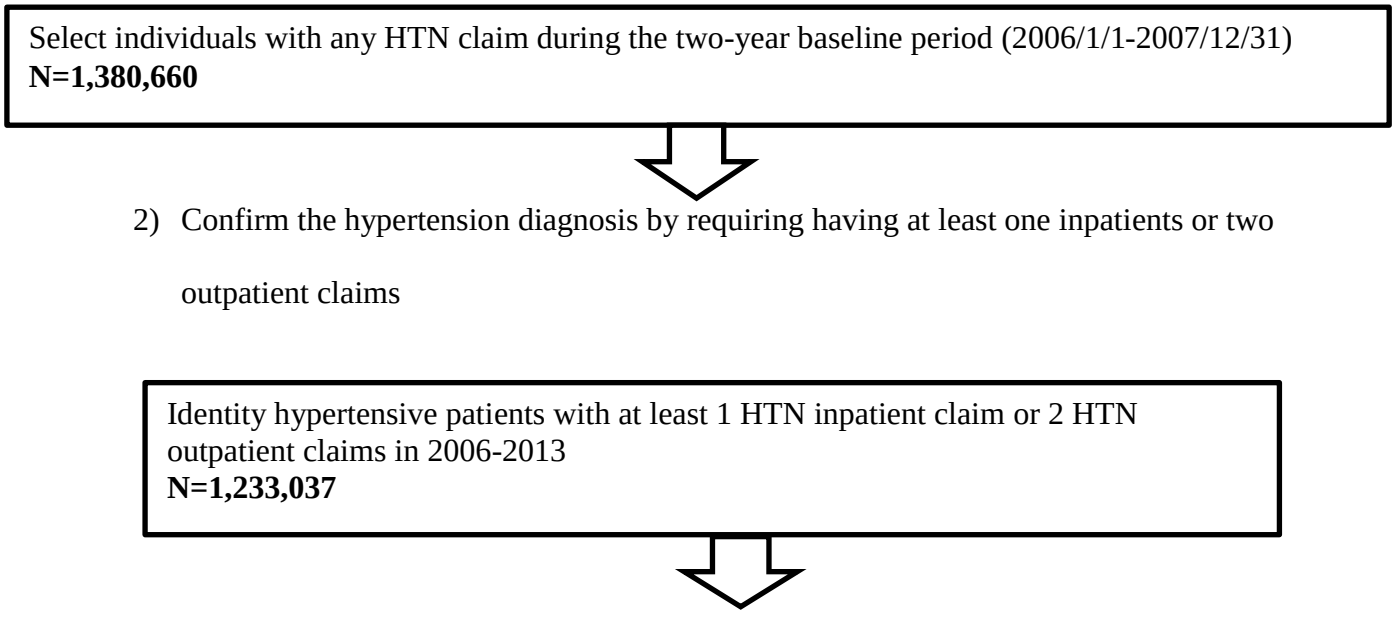
The U.S. Census Bureau provides demographic, social-economic, health insurance coverage and transportation status in a population level based on the ACS 5-Year Estimates[149]. The current information of communities collected by ACS annually helps to determine how federal funding is spent on investments and services. About 3.5 million addresses each year are randomly selected to participate in the survey. The 5- year estimates use 60 months of

collected data which report the most reliable but less current information on communities, and support examining smaller geographies, such as counties[149]. The PCSA data contains nationwide data on the United States primary health care resources and population in zip code level which reflects patient's healthcare utilization[150]. This ecological information were first aggregated to county level by Federal Information Processing Standard (FIPS) county code, and then linked with other environmental data. Map of Centers of Population provides the longitude and latitude of the center for counties in the United States. This type of information is necessary in spatial analysis. In the end, a crosswalk file of FIPS county code and Social Security Administration (SSA) state/county code were created to link these etiology data, spatial data with the Medicare claims. Completely de-identified data were used for study analysis.

3.1.2 Study population

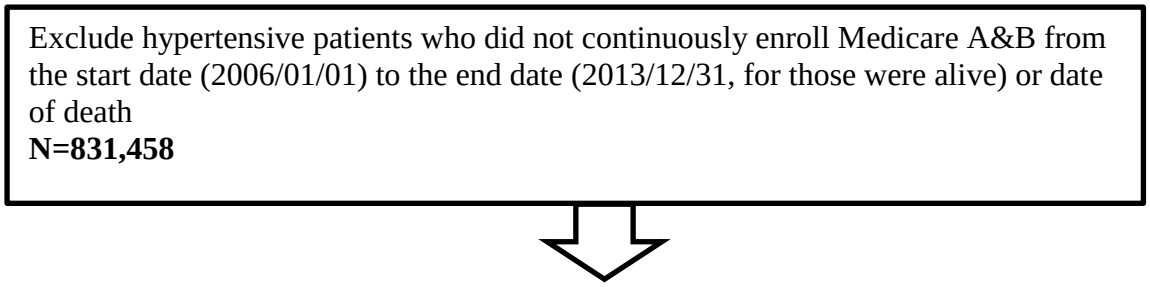
For Aim 1, we followed these steps to extract the study cohort:

1) Start with the 1,380,660 Medicare beneficiaries who had any hypertension (HTN) related claims

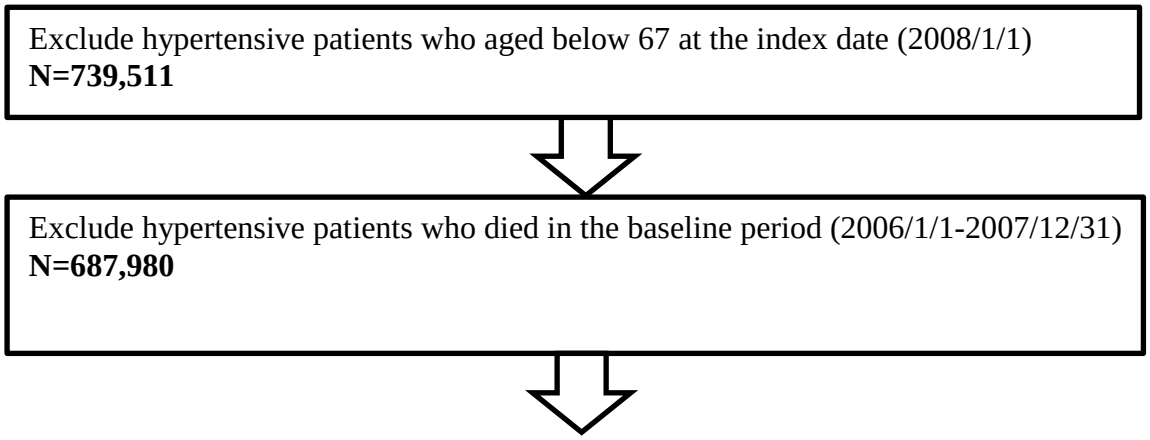


2) Confirm the hypertension diagnosis by requiring having at least one inpatients or two outpatient claims

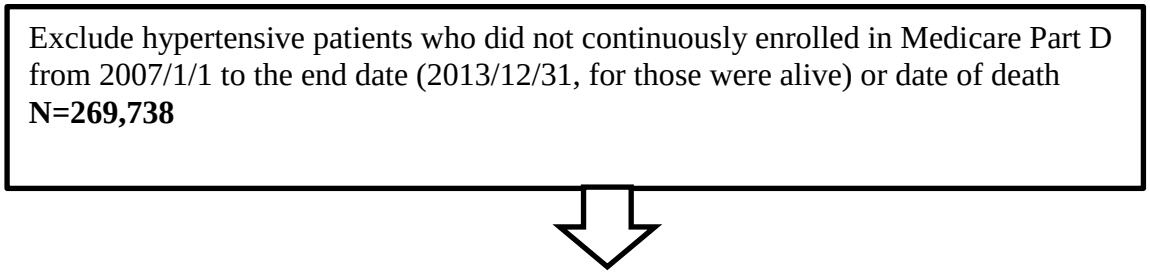
3) Check the Medicare enrollment and exclude those enrolled in Medicare Advantaged Plan



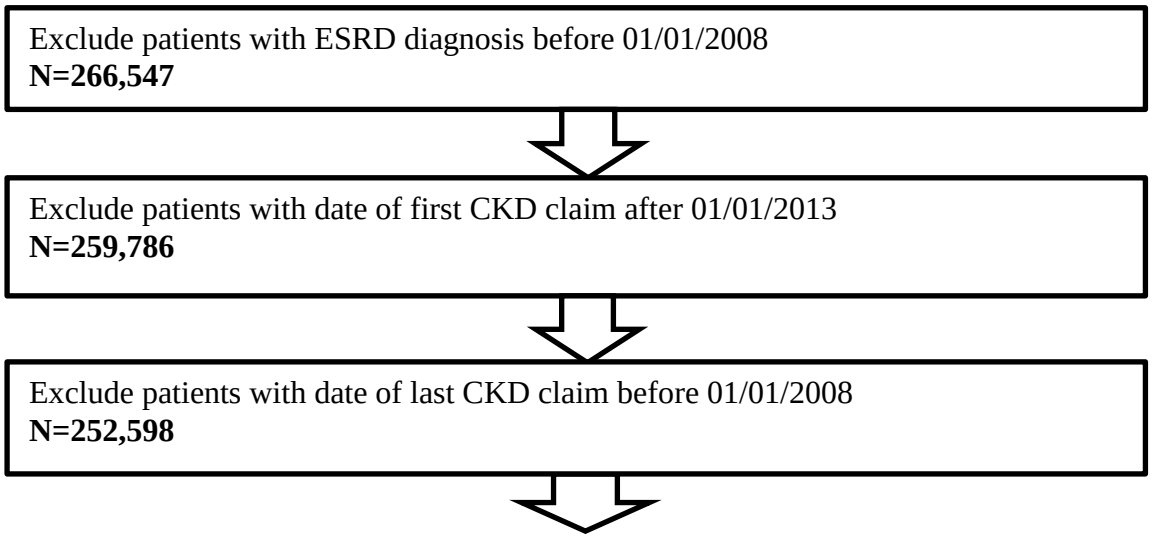
4) Exclude non-elderly Medicare beneficiaries and those who died before the beginning of follow-up period.



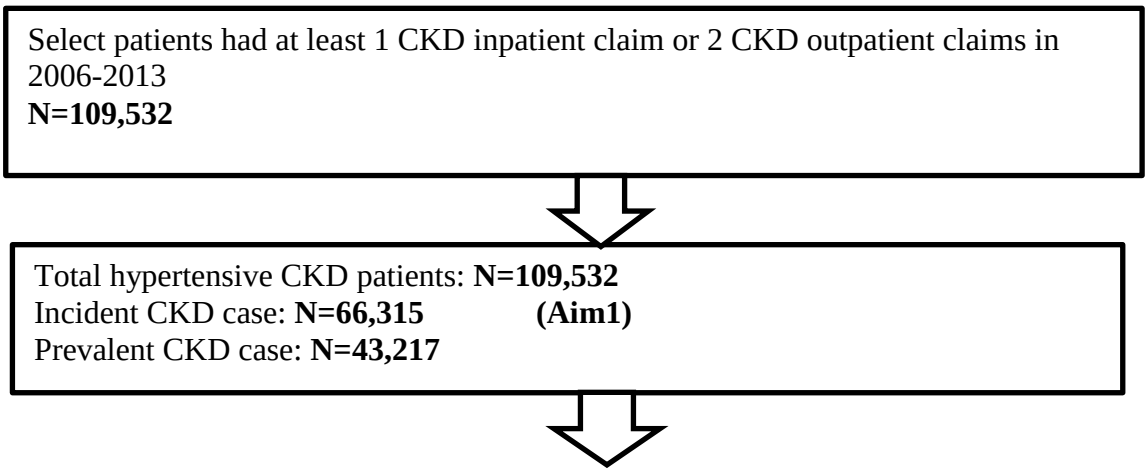
5) Check Medicare Part D enrollment



6) Restrict to subjects based on their ESRD/CKD visits to ensure each of them had at least one year follow-up period



7) Identify hypertensive CKD patients the incident cases were final study subjects for Aim1

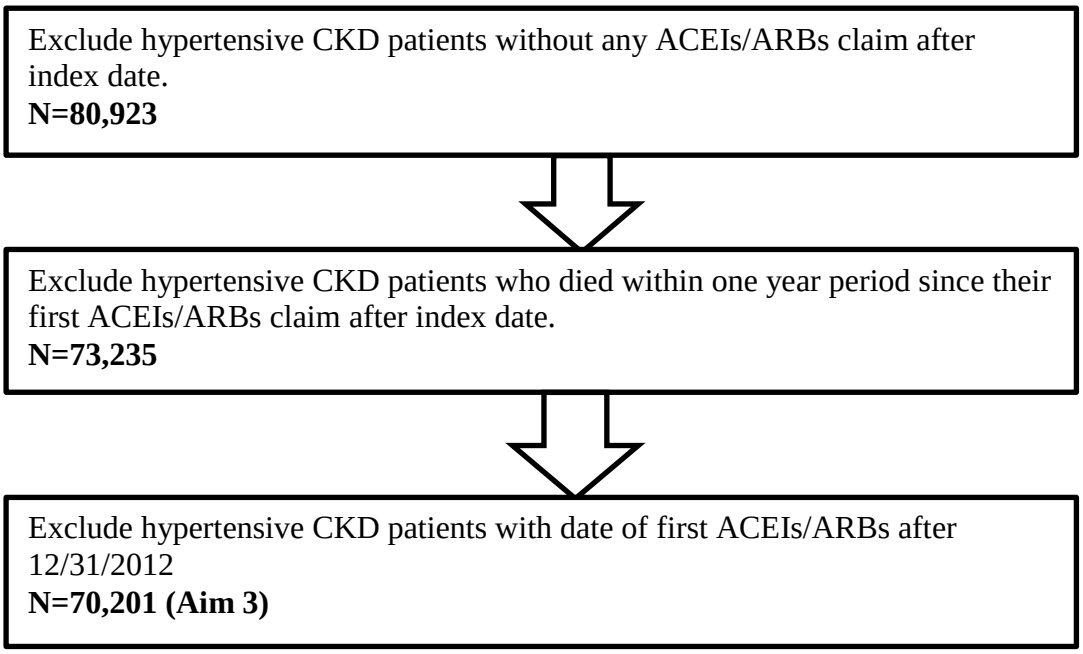


Then we followed additional steps to identify the final study sample for Aim 2 and Aim 3

1) From the total hypertensive CKD patients, select a subset of subjects who had a history of ACEIs/ARBs use

Exclude hypertensive CKD patients without any claims of ACEIs/ARBs within the one-year baseline period
N=65,574 (Aim2)

2) From the total hypertensive CKD patients, select a subset of subjects who had used ACEIs/ARBs in the follow-up period, and had a valid one-year medication adherence.



3.2 Measurement of study variables

3.2.1 Individual-level characteristics

Predisposing Characteristics

Demographic: Medicare 5% sample claims from the USRDS database were the primary resources for demographic information (age, gender and race). Age was calculated based on the birthday and index date (01/01/2008). Race were defined as white, black, Asian, and others.

Enabling Resources

Prescription drug coverage: In this study, all study subjects were enrolled in stand-along Part D plans. To distinguish the different premiums and copayments that the subjects may have, we were further classified them into three categories based on the receipt of a low income subsidy in 2008: Part D with deemed LIS, Part D with non-deemed LIS, as well as Part D without LIS. Beneficiaries with deemed LIS are mainly Medicare and Medicaid dual eligible beneficiaries. They are automatically enrolled in LIS and typically have lowest premiums and copayments compared to the other two groups[151]. For example, beneficiaries with deemed LIS receive a 100% premium subsidy for their prescription drug coverage, and their copayments of covered drugs are reduced to a fixed amount or even eliminated. Beneficiaries who are not Medicare dual eligibles but have incomes below 150% of the Federal Poverty Level are eligible to apply LIS, also called non-deemed LIS beneficiaries. They receive a premium subsidy varing from 25% to 100% of their monthly premium. Meanwhile, they pay up to 15% of expenditures for all Part D covered drugs. It is noteworthy that there is no gap in prescription drug coverage, also known as “donut hole”, in beneficiaries with either deemed or non-deemed LIS.

Need

Comorbidities: Comorbidities at baseline were identified for each study subjects using a two-year observation period (2006-2007) based on the Medicare 5 percent files. We determined comorbidities using the same algorithm that implemented with the USRDS ADR: having at least one inpatient claim or two outpatient claims with specified diagnosis/ procedure codes. The validity and reliability of this method had been examined in previous studies[152]. Inpatient claims include claims of inpatient hospitalizations, skilled nursing facility, and home health service. Outpatient claims include claims of outpatient hospital services and physician/supplier. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code and the Healthcare Common Procedure Coding System (HCPCS) code were used to determine onset of conditions.

Charlson comorbidity index (CCI) was implemented as a comorbidity burden measure in this study. CCI is a previously validated measure to predict mortality. The index calculation involves a total of 22 distinct conditions (heart disease, chronic lung disease, liver disease, acquired immunodeficiency syndrome [AIDS], and so on.), and each of them is assigned a weight score from 1 to 6 based on their association with mortality[153]. An adapted CCI was calculated with exclusion of diabetes, kidney and cardiovascular diseases. Higher CCI indicates greater comorbidity burden, which could be either having multiple comorbid conditions or having severe conditions. Separate indictors were generated for conditions that were closely related with CKD, like diabetes, cardiovascular conditions and cardiovascular procedures.

3.2.2 Contextual characteristics

Predisposing Characteristics

Percentage of population covered by Medicare at county level served as proxy of predisposing characteristics.

Availability

The rate of general physicians per 10,000 persons and percentage of population residing in MUAs at county level served as proxy of availability. These two numbers were extracted from the PCSA data[154].

Enabling resource

Deprivation score was derived from four census variables: percentage of household without car ownership and home ownership, percentage of household overcrowding (more than 1 person per room), and unemployment rate among people aged 16 and over[155]. We first took a log transformation of household overcrowding rate and unemployment rate, and then standardize all four variables. The sum of these four standardized score was Townsend index. A larger positive Townsend index indicates severe deprivation.

3.2.3 Healthcare outcomes

Due to a lack of laboratory test results in Medicare 5% sample claims we cannot measure the course of renal function. Thus, the progression of CKD was defined as being diagnosed with ESRD. The primary outcomes in this study were CKD associated clinical outcomes. The specified measures include being diagnosed with ESRD and all-cause death. In the USRDS database, the date of ESRD is determined by the first service date extracted from the ESRD Medical Evidence form (CMS 2728). Date of death is obtained from the ESRD Death Notification form (CMS 2746) as well as the Master Beneficiary Summary File. We defined a censored date for those who did not experience the specified outcomes within our study

period. When diagnosed ESRD was the interested outcome, we had their data censored when the last CKD-related visit happened. When mortality was the outcome of interest, the censored date referred to the end of our study (Dec 30th 2013).

3.2.4 Medication utilization

In this study, we investigated utilization of ACEIs and ARBs among hypertensive CKD patients, as well as other four most commonly used cardiovascular agents (statins, beta-blockers, diuretics, and calcium channel blockers). Medicare prescription drug event files contain comprehensive information about filled prescriptions, such as the generic and brand name, the corresponding National Drug Code (NDC), supply days of each fill, and the date that the prescription filled. We first found all active ingredients under each of therapeutic drug classes from the website of the Anatomical Therapeutic Chemical Classification System. We then developed a list of NDC codes for each active ingredient based on the National Drug Code Directory from the Food and Drug Administration. Lastly, we identified prescription event for each drug class by matching pharmacy claims against the list of NDCs[156]. Measurement of medication use was varied across study aim1-3. In the next section, we introduced measurement of medication use and statistical analysis for the three study aims.

3.3 Study Aim1: Compare the effects of different pharmacologic therapies on CKD outcomes for hypertensive CKD in Medicare Part D enrollees

Introduction:

Pharmacologic therapies including ACEIs/ARBs are strongly recommended for hypertensive patients with early stage CKD in the clinical guideline developed by the ACP. Meanwhile, there is evidence that statin therapy demonstrates a beneficial effect for hypertensive CKD patients. By analyzing medication prescription patterns and comparing effects of different

therapies on CKD outcomes, our study provided significant information for clinicians when they make CKD treatment decisions.

Research cohort:

We used a subgroup of our hypertensive CKD cohort to assess medication use patterns, that was, elderly hypertensive patients who were newly diagnosed with CKD (as shown in section 3.1.2).

Medication related measures:

Medication use

Dummy variables were created to indicate utilization of each drug class. A value of 1 represented patients having at least 1 pharmacy claim under the specified drug class during the first six months after diagnosis of CKD.

Medication Persistence

Medication persistence reflects the duration of complying with the prescribed drug, calculating as time period from the initiation of the drug to the discontinuation of the drug. Medication persistence has been widely used as a measurement of medication adherence in observational research studies. The definition of discontinuation can be varied from study to study, and it usually determined by the characteristics of conditions and drugs. Generally, the supply days of a cardiovascular agent are one-month or three-month. Thus, we defined non-persistence as a minimum three-month medication fill gap.

Pharmacological therapy patterns

Patients with hypertension and CKD receive either monotherapy or combination therapy to treat their conditions. To explore the effects of different treatment strategies, we grouped the six types of cardiovascular agents investigated in this study into three categories: RAS

inhibiting agents (ACEIs and ARBs), statins, and other antihypertension agents (calcium channel blocker, beta-blockers and diuretics). Therefore, patients were classified into eight different treatment groups according to their medication use status: receiving none of the studied cardiovascular agents; receiving monotherapy of RAS inhibiting agents, statins, or other antihypertension agents; receiving combination therapy that contained any two of the above three categories; as well as receiving combination therapy that included at least one RAS inhibiting agent, one other antihypertension agent plus statin.

A more restricted measure of pharmacological therapy patterns was also developed for sensitivity analyses, which incorporated the concept of medication persistence. To be considered as a qualified user of a specified drug class, patients need to be on the drug for more than three months. Similarly, to be considered as receiving combination therapy, the overlap days of filling individual components should be above 3 months. By using this restricted measure, fewer patients were expected to be classified as receiving combination therapies.

Statistical analysis

Descriptive analyses were conducted by status of ACEIs/ARBs use, presented as mean and standard deviation for continuous variables, as well as frequency and percentage for categorical variables. To assess the characteristic difference between these two subgroups, two-tailed t-tests and chi-square tests will be used for continuous variables and categorical variables. Multivariate Cox regressions were conducted to assess the relationship between pharmacological treatment patterns, onset of ESRD and all-cause mortality.

Logistic regression model was implemented to explore the predictors of receiving ACEIs/ARBs after the first diagnosis of CKD in hypertensive patients.

3.4 Study Aim2: Examine how patients' adherence to ACEIs and ARBs influence their CKD progression, renal failure and mortality by incorporating time varying effect.

Introduction

The progression of CKD is associated with increased healthcare cost and mortality. Several randomized clinical trials in the field of CKD demonstrated use of ACEIs/ARBs had a protective effect on CKD progression and mortality[157,158]. However, few studies have systematically assessed the long-term benefits of ACEIs and ARBs in delaying the progression of CKD and death using claims data[159,160]. The objectives of study Aim 2 was to examine how patients' adherence to RAS inhibiting agents potentially associated with renal failure and mortality among aged patients with hypertension and CKD.

Study population

Hypertensive CKD patients who had used ACEIs/ARBs in the one-year baseline period were selected as eligible study subjects in study Aim2. A history of ACEIs/ARBs use indicated that ACEIs/ARBs were applicable to these patients, and they ought to be adherent to the prescribed ACEIs/ARBs (illustrated in section 3.1.2).

Medication related measures:

Medication adherence

We used the Proportion of Days Covered (PDC) to quantify medication adherence behavior in this study. PDC is widely used as a measure of medication adherence for analyses using secondary database. PDC is defined as the proportion of number of days covered by the prescription fills within a given period. When using PDC as a proxy of medication adherence, we assumed that medications were taken by patients during the supplied days.

We defined a refill interval began with the date of first pharmacy claim within each drug class and ended with the last date of observed period. For example, we used the last date of baseline period to calculate baseline medication adherence, while used the end date of our study /date of death to calculate the follow-up medication adherence. The PDC was computed as the total days supply for each drug class divided by total days in the refill interval. The total days supply for each drug class was calculated by the sum of total days supply for the specified drug class subtracting their overlap days. Adherence can be presented using the following equation:

$$PDC(\%) = \frac{Total\ \ days\ supply\ for\ all\ pharmacy\ claims\ within\ the\ specified\ drug\ class - \ Overlap\ days}{End\ date\ of\ observed\ period - First\ date\ of\ despensing\ the\ specified\ drug\ class},$$

Time-varying medication adherence

To develop a time-varying measurement of medication adherence, PDC was measured quarterly from the index date (01/01/2008) to the end date (12/31/2013 or date of death). Thus, the denominator of the above equation was fixed to 90 days, except for the last quarter in patients who died in our study period.

Statistical analysis

We defined a censored date for those who do not experience the specified outcomes within our study period. Patients were censored at the date of the CKD related visit when ESRD was the investigated outcome, while patients were censored at the end of our study (Dec 30th 2013) when assess overall survival time. To calculate the relative risk of developing our specified outcomes, we used multivariate Cox regression modeling with delayed entry. Since

medication use was a time-varying covariate, the model was presented as the following equation:

$$\lambda_i(t, PDC\ of\ ACEIs_i(t), PDC\ of\ ARBs_i(t),\ PDC\ of\ OtherRx_i(t),) =$$
$$\lambda_0(t)\exp\{\beta_1(t)PDC\ of\ ACEIs_i(t) + \beta_2(t)PDC\ of\ ARBs_i(t) + \beta_3(LIS\ status) +$$
$$\beta_4(baseline\ age) + \beta_5(gender) + \beta_6(race) + \beta(t)PDC\ of\ OtherRX_i(t) +$$
$$\beta(other\ covariates)\}$$

Where t represented the ESRD free time or overall survival. $\lambda_0(t)$ referred to the common baseline hazard for all subjects. $PDC\ of\ ACEIs_i(t)$, $PDC\ of\ ARBs_i(t)$ and $PDC\ of\ OtherRx_i(t)$ were time-varying covariates representing the characteristics of medication use for individual i at time t. $\exp(\beta_1(t))$ and $\exp(\beta_2(t))$ were the time-dependent parameters of interest, representing the adjusted hazard ratio of 1 unit change in these characteristics at time or duration t. We also controlled subjects' demographic characteristics at baseline, including age, gender and race. Other potential covariates included: baseline indicators of enabling resource (health insurance coverage) and baseline comorbidity indicators (CCI scores, diabetes, as well as common cardiovascular diseases and procedures). We tested the proportional hazard assumption through scaled Schoenfeld residuals, and use the model fit statistics for model comparison and selection. The statistical significance level is $p < 0.05$.

3.5 Study Aim3: Model ACEIs/ARBs adherence as a function of individual and contextual factors among aged hypertensive patients with CKD in the United States.

Introduction

Despite the benefits of ACEIs/ARBs in CKD progression and renal event, medication adherence among CKD patients need to be further improved. An observational study found 33% of CKD patients had poor medication adherence to antihypertensive agents[4]. In study Aim3, we assessed elderly hypertensive CKD patients' adherence to ACEIs/ARBs across different geographic region, and explore preventable and modifiable risk factors for medication adherence.

Research cohort

We extracted a subgroup of our hypertensive CKD cohort to assess one –year medication adherence, which was, patients who had at least one pharmacy claims for an ACEI or an ARB in the follow-up period. Subjects who died within one year period from their first ACEIs/ARBs claim during the follow-up period, and those who initiated their ACEIs/ARBs after 12/31/2012 were excluded (illustrated in section 3.2).

Medication related measures:

One-year ACEIs/ARBs adherence

According to the clinical practice guideline in CKD, both ACEIs and ARBs should be used at moderate to high doses for CKD patients, and they can be used as alternatives to each other when the preferred class cannot be used[42]. Thus, in the study Aim3, ACEIs and ARBs were combined together when we computed PDC. Adherence to ACEIs/ARBs was calculated in the form of PDC with one year fixed refill interval starting from the first date of dispensing ACEIs/ARBs. Thus, the equation of PDC was total days covered by ACEIs/ARBs in the one-year refill interval divided by 365. By using the fixed refill interval, we were able to adjust discontinued therapy.

Statistical analysis

For descriptive analyses, we first stratified patients into two groups: PDC greater than 80%, and PDC below 80%, which was the most widely used threshold for medication adherence[161]. Descriptive data including means, standard deviation, frequencies, and percentages were calculated for each group. Two-tailed t-tests for continuous variable and chi-square tests for categorical were used for group comparison.

GWR was conducted to investigate the association between contextual factors and medication adherence at county level using GWR4 software. First, we aggregated the PDC of ACEIs/ARBs to the county level, and then conducted Moran's I test. A statistically significant Moran's I test indicated the existence of spatial autocorrelation in county-level mediation adherence. We then applied a multivariate linear regression model to establish a properly specified model for GWR. The model can be described by the following equation:

$$Y(aggregated\ adherence\%) = \beta_0 + \beta_1(rate\ of\ general\ physician) + \beta_2(\%\ of\ population\ residing\ in\ MUAs) + \beta_3(Deprivation\ score) + \beta_4(\%\ of\ Medicare\ beneficiaries)$$

Second, we checked the redundancy among our explanatory variables using Variance Inflation Factor (VIF) value. Variable with the largest VIF value were removed one by one until all variables' VIF value below 2. The adjusted R squared value refers how much of the variance in medication adherence are explained in our model. Third, we performed a GWR model and examine the changes in goodness-of-fit using R^2 and the Akaike Information Criterion (AICc). In addition, we also evaluated the performance of GWR model with

ordinary least squares (OLS) model through GWR ANOVA test. A significant F value indicates GWR is preferred to the OLS model.

Different from OLS, GWR is able to provide results of local regression model for each independent variable and each geographical location. By doing that, researchers first define a circle of some radius around a particular patients' location p_i, called kernel (in our case, center of population at county level), and then run a local OLS regression model only on the basis of patients located within the circle. Thus, the coefficient β_{ij} will be interpreted as an estimated association between independent variable j and medication adherence in and around location p_i. A weight will be assigned to each patient in the circle by the kernel functions, which can be described by the following equation[162]:

$$a_{ik} = \begin{cases} \{1 - (d_{ik}/h)^2\}^2 & If\ d_{ik} < r, \\ 0 & otherwise \end{cases}$$

Where a_{ik} is the weight assigned to patient k when location of patient i (p_i) is the center of the kernel; d_{ik} is the distance between patient k and i; h refers to the kernel bandwidth; and r stands for the radius of the circle. The constant variable r and h control the size of the circle and the range of the "circle of influence" of the geographical data. In this study, the Gaussian kernel was used to define r: r was smaller where patient distribution was denser, and r was larger when patient distribution was sparse. The AICc wass used to determine h. Lastly, we conducted geographical variability test for each of our explanation variables. A positive value of "DIEF of Criterion" indicate there is not significant spatial variation in the local estimates of the investigated explanation variable, and the variable is preferred to treat as global variable rather than local variable. In the end, virtualized maps were developed by SAS software to display results of GWR analyses.

We further conducted a mixed effect model to assess the association between individual factors, contextual factors, and medication adherence, controlling random effects of county factors. All individual level variables were included in this model based on our conceptual model. The statistical significance level is $p<0.05$.

Chapter 4

DISSERTATION MANUSCRIPT ONE: Comparison of effects of different pharmacologic therapies on chronic kidney disease (CKD) outcomes in Medicare Part D enrollees with hypertensive CKD

4.1 Abstract

OBJECTIVES: Little research has evaluated cardiovascular agents use patterns in CKD patients and compared effects of different pharmacologic therapies on CKD outcomes. This study aimed to assess medication use patterns in elderly patients with hypertensive CKD in the United States. Associations between different anti-hypertensive regimens and CKD outcomes were investigated.

METHODS: We used Medicare 5% sample claim data from the USRDS database (2006-2013) in this retrospective study. Eligible cases were hypertensive patients who were newly diagnosed with CKD and continuously enrolled in Medicare stand-alone Part D plans. We investigated six drug classes: ACEIs, ARBs, other anti-hypertensive agents (calcium channel blockers/ beta-blockers/ diuretics), and statins. Medication use was defined as having at least one pharmacy claim within each drug class during a six-month period after the date of first diagnosis of CKD. The multivariate Cox regression model was used to assess effects of different pharmacologic therapies on progression to end-stage renal disease (ESRD) and

death. Logistic regression was used to explore factors that were associated with using guideline-recommend ACEIs/ARBs.

RESULTS: About 32,973 of the 66,315 incident hypertensive CKD patients (50%) were using ACEIs/ARBs within six months after the diagnosis of CKD. Approximately 5.2% of patients received ACEIs/ARBs monotherapy, while 4.4%, 17.5% and 22.7% of them received the following combination therapies: ACEIs/ARBs plus statins, ACEIs/ARBs plus other anti-hypertensive agents, and all of the above three therapeutic groups. Compared to combination therapy of statins and other anti-hypertensive agents, therapies adding ACEIs/ARBs showed a significantly decreased risk of ESRD and death (HR=0.69, p=0.0115; HR=0.88, p<0.0001). Additionally, the risk of ESRD and mortality was reduced by 0.53 and 0.85 when substituting other anti-hypertensive agents plus statins with ACEIs/ARBs plus statins (HR=0.53, p=0.0112; HR=0.85, p<0.0001).

CONCLUSIONS: Use of guideline-recommended ACEIs/ARBs were suboptimal in elderly patients with hypertension and CKD. Therapies including ACEIs/ARBs were preferred as initiation therapy than non-ACEIs/ARBs therapies in hypertensive CKD. Regimens including ACEIs/ARBs and statins were associated with reduced risk of ESRD and death. These findings may provide evidence for clinicians when they select pharmacological treatments for elderly patients with hypertension and CKD.

4.2 Introduction

Chronic kidney diseases (CKD) is becoming a major worldwide public health problem[13,14]. In the United States, the prevalence of CKD in the general population is 15%, estimated based on participants from NHANES 2011-2014, a large nationally representative sample[1]. Old adults are particularly at high risk of CKD, as one-third of NHANES participants aged 60 and older have CKD[1]. Decline of renal function is associated with several serious complications, like anemia, mineral and bone disorders, and cardiovascular conditions, as well as increased risk of mortality[22,43,52,163]. Therefore, CKD and its consequent kidney failure, also known as ESRD, pose a significant burden on patients and their families, as well as the healthcare system. As reported by the United Sates Renal Data System Annual Data Report (USRDS ADR), the overall Medicare expenditures for CKD and ESRD have continuously increased over time and reached $52.8 billion and $32.8 billion in 2014, accounted for 21% and 7.2% of total Medicare expenditures respectively.[1].

Hypertension is the second leading cause of kidney failure in the United States[39]. Approximately 74% of CKD patients in the United States had co-existing hypertension[1]. Moreover, previous studies had revealed that uncontrolled blood pressure may accelerate the progression of CKD[164,165]. Unfortunately, individuals with CKD were at a higher risk of uncontrolled blood pressure compared to those without CKD[86,166,167]. High prevalent of uncontrolled blood pressure may attributable to the different underlying cause for hypertension and the suboptimal utilization of anti-hypertensive agents. The current research revealed that CKD patients had a greater drug burden than the general population[88]. For example, two previous CKD studies showed their investigated cohorts took an average of eight different medications and 6.7 pills daily respectively[92,121]. In particular, more than half of CKD patients received polypharmacy to control their blood pressure, and a certain

proportion of CKD patients took three or more different anti-hypertensive agents[4,91]. The complexity of regimen and the heavy pill burden were previously established risk factors of medication compliance[121,132–134]. Thus, examining medication use pattern of medication and comparing the effect of different strategies on CKD outcomes may provide significant information for clinicians to reduce the total number of medications and develop personalized anti-hypertensive regimens for patients with CKD and hypertension.

Despite the important role of anti-hypertensive agents in CKD treatment, few studies have examined the medication use pattern in this population[89,91,92]. A study by Kalyani et al. assessed the utilization of common anti-hypertensive agents using NHANES data and found anti-hypertensive agents, especially ACEIs and ARBs were under used among CKD patients[91]. However, this study did not investigate the combination therapies, and the precision of the measurement for medication use pattern might be limited by the inherent characteristics of self-report measures. In addition, this cross-sectional study did not compare the treatment outcomes between patients receiving different anti-hypertensive regimens.

The purpose of this study is to examine the medication use pattern of cardiovascular agents among elderly patients with CKD and hypertension in the United State. Moreover, we also investigated the relationship between different anti-hypertensive therapies and long-term treatment outcomes. We then explored the factors associated with using guideline-recommended ACEIs/ARBs. Besides ACEIs and ARBs, other four different types of cardiovascular agents that were most commonly used in individuals with CKD were studies: statins, beta-blockers, calcium channel blockers and diuretics. To achieve our study

goals, we restricted our study cohort to incident CKD patients and examine their medication use within the first six-month after diagnosis of CKD.

4.3 Methods

4.3.1 Study design and data source

To achieve the study objectives, we conducted a retrospective cohort study among older hypertensive patients with newly diagnosed CKD using data on the 5% Medicare cohort from the USRDS databases (2006-2013). The Medicare 5% files from the USRDS databases mainly consist of data from the CMS Medicare 5 % SAFs. These files contain comprehensive information on demographic characteristics, Medicare enrollment status, diagnoses, procedures, and filled prescription for a random 5% sample of Medicare beneficiaries across the United States over time. In the USRDS databases, the Medicare claims are further linked to data extracted from the ESRD Medical Evidence form (CMS 2728), the ESRD Death Notification form (CMS 2746) as well as the Master Beneficiary Summary File to obtain information on ESRD and death.

This study design comprised a 2-year baseline period that began from 01/01/2006 to 12/31/2007 to assess patients' history of morbidities and procedures. Meanwhile, a 1-year baseline period was applied to assess patients' history of prescription drug use (year of 2007). Eligible incident CKD patients were identified in the selection period (01/01/2008 – 12/31/2012), and were followed from the date of the first CKD diagnosis to the date of death or the end of our study (12/31/2013).

4.3.2 Study population

Our study samples were selected based on a series of inclusion and exclusion criteria. Among the 1,233,037 Medicare beneficiaries who were diagnosed with hypertension in the 2-year baseline period, we included those who continuously enrolled in both Medicare Part A and B, and were not enrolled in a Medicare Advantage plan (Part C) from the beginning of 2006 to the date of death or the end of this study. To obtain all claims for prescription drugs, continuously enrolled in Medicare Part D from the beginning of 2007 to the end of this study was also required. In addition, we restricted our cohort to aged Medicare beneficiaries by excluding those who aged below 67 by the end of baseline period (12/31/2007), and those who died in the baseline period. Then, we selected hypertensive CKD patients by including those with at least one CKD inpatient claims or two outpatient claims during the study period. To ensure that we followed each study subject for a period of at least one year, we excluded patients who developed ESRD in the baseline period, and those with date of the first observed CKD claim after 01/01/2013/, and date of the last observed CKD claim before the end of the baseline period. Lastly, we extracted a subset group of hypertensive patient with incident CKD who had no CKD related claims in the baseline period.

4.3.3 Measures

Survival outcome measures

ESRD free time was calculated as the time from the date of first CKD claim to the starting date of ESRD. The date of ESRD initiation for our study subjects was determined by the date of first ESRD service extracted from the CMS 2728 form. Subjects who did not progress to ESRD in our study period were censored at the date of death or the date of the last CKD related visits, the date they were last known to be alive and ESRD free. Overall survival

referred to the time from the date of first CKD claim to date of death from all cause. Subjects, who were alive until 12/31/2013, were censored on that date.

Medication related measures

The present study investigated six types of cardiovascular agents that were most commonly used by Part D enrollees with CKD: ACEIs, ARBs, statins, diuretics, calcium channel blockers and beta-blockers. Medication use of each drug class was captured by a binary variable, with 1 indicating at least one pharmacy claim within the specified drug class in the first 6 months of CKD diagnosis. To further assess different therapeutic strategies of cardiovascular agents in hypertensive CKD patients, ACEIs and ARBs were considered together as RAS blocking agents, meanwhile diuretics, calcium channel blockers and beta-blockers were grouped together named as other anti-hypertensive agents. Therefore, patients were classified into a total of eight different treatment groups: using none of studied prescriptions, using statins only, using RAS blocking agents only, using other anti-hypertensive agents only, as well as using any combination of these agents.

To test the robustness of our study results, we also developed a restricted measurement of medication use pattern, which is intended to capture "true" overlap as distinct from medication switches. To be qualified for receiving polypharmacy, the overlap days of receiving each component of the specified combination therapy should be greater than 3 months within the 6 months observation window. Meanwhile, the start date and the end date of each prescribed medication were determined by medication persistence with an allowed 90-day medication fill gap.

Covariate measures

Demographic information on age, gender and race was obtained from the Medicare 5% sample files. Age was measured as both a continuous variable and a categorical variable with four levels. Race was captured as a categorical variables as white, black, Asian, others and unknown. Part D coverage was determined by subjects' enrollment status at baseline. Patients who had at least one calendar month in 2008 with Part D enrollment and receipt of the low-income subsidy (LIS) were classified as "Part D with LIS", otherwise were classified as "Part D without LIS". Among patients receiving LIS, those who were automatically qualified for LIS and automatically eligible for benefits were further classified as "with deemed LIS", while the rest were classified as "with non-deemed LIS". The presence of comorbidities at baseline was determined by a previously vailed method: having a qualifying diagnosis/ procedure code of ICD-9-CM and HCPCS on at least one inpatient claims or two outpatient claims within the 2-year baseline period. Separate indicators of diabetes, common cardiovascular conditions and procedures were created following the same method described above. An adapted Charlson comorbidity index was calculated serving as a measurement of the overall comorbidity burden. We calculated the Deyo CCI with exclusion of diabetes, renal and cardiovascular conditions[168].

4.3.4 Statistical analyses

We first stratified the study population into two groups based on whether or not using ACEIs/ ARBs during the first 6 months after CKD diagnosis. Then we conducted descriptive analyses of demographic factors, cardiovascular conditions and procedures, as well as medication use related factors. The difference of patients' baseline characteristics between ACEIs/ARBs users and non-ACEIs/ARBs users were examined using

chi-square tests and two-tailed t-tests for categorical variables and continuous variables separately. The Cox proportional hazard model was utilized to examine the association between different treatment strategies and progression to ESRD, as well as overall survival. The multivariate logistic model was applied to explore the predictors of receiving ACEIs/ARBs. Moreover, sensitivity analyses were conducted to handle the potential measurement errors and uncertainty due to the definition of medication use. The more restricted measurement of medication use pattern was developed and used in the Cox proportional hazard models.

4.4 Results

Our study population comprised a total of 66,315 aged Part D enrollees with hypertension who had been newly diagnosed with CKD. Approximately half of our study samples received pharmacological therapies including ACEIs/ARBs within the first 6 months after CKD diagnosis. Table 4-1 and 4-2 showed the descriptive statistics for individual demographic characteristics and cardiovascular-related characteristics by patients' status of ACEIs/ARBs use. All eligible patients were followed for a period of 4.5 years, on average, while patients who used ACEIs/ABRs demonstrated a significantly longer follow-up period (5.0 years vs. 3.9 years), a lower death rate (41% vs. 66%), and a higher rate of progression to ESRD (1.1% vs.0.9) compared to those who did not receive ACEIs/ARBs. The average age of ACEIs/ARBs users was 2 years younger than non-ACEIs/ARBs users, at 78.3 years old vs. 80.3 years old. Particularly, compared with non-ACEIs/ARBs users, significantly fewer ACEIs/ARBs users aged 80 and over (40% vs. 52%), and significantly more ACEIs/ARBs users aged below 70 (13% vs. 10%). The majority of our study subjects were white and nearly 38% of them were male. Non-ACEIs/ARBs users demonstrated a noticeably heavier overall comorbidity burden, as their Charlson index was 1.3 times higher than ACEIs/ARBs

users (1.3 vs. 1.0). However, more ACEIs/ ARBs users than non-ACEIs/ARBs users had been diagnosed with diabetes at baseline. In term of prescription drug coverage, more patients who received ACIEs/ARBs were covered by Part D without any subsidy (35% vs. 38%), and fewer of them covered by non-deemed LIS (33% vs. 36%), compared to non-ACEIs/ARBs users. With regards to cardiovascular-related characteristics, significantly more ACEIs/ARBs users than non-ACEIs/ARBs users had presence of atherosclerotic heart disease (ASHD, 45.2% vs. 44.5%), acute myocardial infarction (AMI, 9.6% vs 9.0%), and had received procedures of percutaneous coronary interventions (PCI, 3.3% vs. 2.5%). Nevertheless, a noticeable smaller percent of ACEIs/ARBs users had onset of congestive heart failure (CHF, 26.8% vs 28.5%), cerebrovascular accident/transient ischemic attack (CVA-TIA, 27.1% vs.29.6%), peripheral arterial disease (PAD, 31.7 vs.35.2%), and atrial fibrillation (AFIB, 18.1% vs. 21.1%).

Table 4-3 described the patterns of cardiovascular agents use in hypertensive patients with incident CKD. Patients with receipt of ACEIs/ARBs have a higher level of drug burden, as the mean number of prescribed cardiovascular agents among them was more than 3 times greater than their counterparts without receipt of ACEIs/ARBs (2.5 vs 0.8). The percent of using any other anti-hypertensive agents in ACEIs/ARBs users was about 1.7 times greater than non-ACEIs/ARBs users, more specifically, 1.6, 1.9 and 2.4 times greater in term of receiving beta-blockers, calcium channel blockers and diuretics. Similarly, percent of using statins in ACEIs/ARBs users was nearly two-fold greater than non-ACEIs/ARBs users. Overall, about one quarter of our study subjects received none of studied cardiovascular agents during the first 6 months after being diagnosed with CKD, while approximately half of them received combination therapies which included at least two of the following three distinct therapeutic groups: RAS blocking agents, other anti-hypertensive agents, and statins.

Among those who received monotherapy, a majority of them received one drug of other anti-hypertensive agents to regulate their blood pressure.

Table 4-4 and 4-5 presented the results of the Cox proportional hazard models, which assessed the relationship between different pharmacologic therapies and progression to ESRD, as well as all-cause mortality. Compared to patients receiving combination therapy of statins and any other anti-hypertensive agents, patients who received an additional drug of RAS blocking agents had a 0.31 lower risk of developing ESRD (HR=0.69, p=0.0115) and a 0.12 lower risk of death (HR=0.88, p<0.0001). In addition, the risk of CKD progression and death was reduced by 0.53 and 0.85 when compared combination therapies of other anti-hypertensive agents plus statins to combination therapies of ACEIs/ARBs plus statins (HR=0.53, p=0.0112; HR=0.85, p<0.0001). When compared with monotherapy, therapies including any other anti-hypertensive agents plus statin performed better than monotherapies of other anti-hypertensive agents in both delaying disease progression and death (HR=1.63, p=0.0015; HR=1.31, p<0.0001), while no significant difference were observed when compared with monotherapy of statins (HR=0.67, p=0.1742; HR=1.05, p=0.1696). Moreover, compared to combination therapies with any other hypertensive agents plus statins, monotherapies of ACEIs/ARBs were associated with a lower risk of onset of ESRD but a higher risk of being died (HR=0.57, p=0.0399; HR=1.14, p<0.0001).

Table 4-6 showed factors that significantly associated with use of ACEIs/ARBs during the first 6 months after CKD diagnosis. On one hand, patients who were older, male, having higher Charlson comorbidity index, receiving deemed LIS, having occurrence of CVA-TIA, PAD and AFIB were less likely to receive pharmacological therapies with ACEIs/ARBs

when they were diagnosed with CKD. On the other hand, patients who were nonwhite, having diabetes and ASHD, as well as receiving PCI were more likely to receive ACEIs/ARBs on time.

Results of sensitivity analyses indicated that the risk factors of progression to ESRD remained stable when we extended the censored date from last CKD visits to the end of our study. We also re-estimated our models using the restricted measure of therapeutically patterns which incorporated the concept of medication persistence and added a requirement of having at least 90 days of overlap for each individual drug under the specified combination therapy. When employing the restricted measurement of treatment patterns, as we expected, more patients were classified as received none of investigated cardiovascular agents (increased from 25% to 31%), and fewer patients were classified as receiving all of the three drug groups (from 46% to 12%). With regards to the changes in the results of survival models (shown in table 4-7 and table 4-8), therapies consisted of drugs from all three therapeutic groups persistently showed better survival outcome of progression to ESRD and death than the comparison group, combination therapies of other anti-hypertensive agents and statins (HR=0.58, p=0.0015; HR=0.78, p<0.0001). Monotherapies of other anti-hypertension agents constantly performed worse than the comparison group in delaying disease progression and reducing mortality (HR=1.93, p<0.0001; HR=1.54, <0.0001). However, performance of monotherapy of statins on mortality became worse when compared with the comparison group (HR=1.6, p<0.0001). Meanwhile, monotherapies of RAS inhibitors and combination therapies of RAS inhibitors plus statins did not show a significant survival benefit on ESRD anymore (HR=1.2, p=0.4388; HR=0.9, p=0.5991). In term of overall survival, monotherapies of RAS inhibitors continuously showed an increased risk of death compared to the comparison group (HR=1.7, p<0.0001), and combination therapies of RAS inhibitors plus

statins had a marginally significant decreased risk of death than the comparison group (HR=0.9, p=0.0892)

4.5 Discussion

The lack of knowledge about utilization patterns of cardiovascular agents and the effect of different anti-hypertensive therapies among hypertensive CKD patients may limit our ability to reduce the pill burden and improve treatment outcome in this population. Thus, this study assessed different anti-hypertensive therapies of the six most commonly used cardiovascular agents among patients with hypertension and CKD. Moreover, compared with previous studies, our study had strengths as a large study cohort extracted from nationally representative claim data and relatively long study duration. These strengths enabled the assessment of differences in direct outcome such as progression to ESRD and all-cause mortality.

Overall, this study found 78% of hypertensive CKD patients were on at least one type of cardiovascular agents when they were newly diagnosed with CKD. Consistent with previous studies, heavy pill burden was observed in our hypertensive CKD cohort as well[88]. More than two-third of hypertensive CKD patients who received cardiovascular agents were observed on combination therapies: receiving at least two drugs of the following three therapeutic groups—RAS inhibitors (ACEIs/ARBs), statins, and other anti-hypertensive agents (beta-blockers, diuretics, and calcium channel blockers). However our study found a lower utilization rate in all of investigated drug classes compared to the utilization rate of cardiovascular agents reported in the USRDS report[1]. This may attributable to the relatively older population and a shorter medication assessment window (the first 6 months after first

diagnosis of CKD). Overall, only half of our study subjects were on guideline-recommended ACEIs/ARBs after being diagnosed with CKD. It was noteworthy that this utilization rate remained low in patients with onset of diabetes (56%), despite the fact that clinical evidence found ACEIs/ARBs have additional renoprotective benefits for CKD patients[95,96]. Our findings revealed that there was a potential improvement for ACEIs/ARBs use in CKD patients.

We further assessed the association between different pharmacological therapies and CKD outcomes, which were not evaluated by previous studies because of short observation period (1-2 years) and lack of claim data[91,92]. In the present study, comparison group was set as combination therapy of statins and other hypertensive agents that were not substituted for ACEIs/ARBs. Our results found that patients who received ACEIs/ARBs as add-on therapies were significantly less likely to progression to ESRD and had a lower risk of death, compared with the comparison group. Moreover, with the fixed number of prescribed medications, replacing the other anti-hypertensive agents with ACEIs/ARB in the comparison group may reduce the risk of developing ESRD and death. However, replacing statins with ACEIs/ARBs in the comparison treatment did not result in better CKD outcome. When compared to monotherapies with the comparison treatment, we found adding statins to the monotherapy of other anti-hypertensive agents yielded a better CKD outcome. Overall, our results illustrated pharmacologic therapies including ACEIs/ARBs and statins demonstrated substantial benefits to elderly patients with hypertension and CKD than those without ACEIs/ARBs and statins. Findings of this observational study provide real-world evidence for the guidelines from APC: selecting anti-hypertensive regimens including statins for patients with mild to moderate CKD and including ACEIs/ARBs for those with hypertension. Moreover, our findings indicated that the priority of ACEIs/ARBs and statins may be higher than other

hypertensive agents. And this information is meaningful from a clinical perspective, since providing an anti-hypertensive regimen with minimized number of drugs have significant benefits in term of overall pill burden, complexity of administration, medication adherence, efficacy, side-effects and adverse effects[169–171].

Receiving ACEIs/ARBs when diagnosed with CKD may related to multiple factors including: younger ages, female sex, nonwhite race, less comorbidity burden, without Part D low income subsidy, presence of diabetes and ASHD, receiving PCI, as well as without onset of CVA-TIA, PAD and AFIB. Kalyani et al explored the predictors of receiving anti-hypertensive treatment in CKD patients and found patients who were older, male, white, aware of hypertension and diabetes were more likely to use anti-hypertensive agents. The inconsistent association in demographic factors may because of distinct study populations and types of measurements. We also found patients who were automatically enrolled in Part D LIS program were less likely to receive recommended ACEIs/ARBs, even though they had the lowest premiums and copayment, and no coverage gap in prescription drug coverage. These patients are mainly dual-eligible patients (Medicare and Medicaid). The significantly suboptimal utilization rate of ACEIs/ARBs may indicate the existence of barriers to accessing recommended prescriptions beyond cost in this vulnerable population.

The present study was limited in several ways. First, the retrospective cohort study design cannot establish a causal inference between utilization patters of cardiovascular agents and CKD related outcomes. Second, the Medicare claim data lack laboratory values, thus we were not able to assess the severity of renal dysfunctions and whether blood pressure was under controlled at the time they first diagnosed with CKD. These two factors are associated with

the selection of cardiovascular agents as well as number of drugs[172,173]. Third, the precision of medication use measures was limited by the characteristics of pharmacy claims data. In this study, we assumed that Medicare Part D was the only source of medications, which may not be the true in all circumstances. For example, Medicare beneficiaries may use their commercial prescription drug coverage to get their ACEIs/ARBs filled, which would not be reflected in Medicare claims data. Meanwhile, how to determine combinational therapies is challenging, especially considering changes in treatment strategies over time (switching, adding on and discontinuation). In this study, we implemented two methods to capture utilization patterns: 1) having any billed pharmacy claims; 2) incorporating the concept of medication persistence and adding requirement of over-lap more than 3 month in the 6 month observation window. As expected, the second method identified more non-cardiovascular agents users and monotherapy users, while identified less combinational therapy users. It is worth to note that the results of our sensitivity analyses indicated that therapies adding ACEIs/ARBs and statins demonstrated a steady substantial benefits compared to therapies without ACEIs/ARBs in delaying CKD progression and improving overall survival, with adjustment of demographic, medical history, and health plan characteristics. Lastly, the generalizability of our study is limited by our study design. In this study, eligible subjects are hypertensive patients with newly diagnosed CKD who were covered by Medicare stand-alone Part D plans. Medicare beneficiaries who received prescription coverage from the Medicare Advantage plan were excluded in this study. Moreover, results of our study may suffer selection bias due to the restricted selection criteria. For instance, to capture all pharmacy claims, only beneficiaries who continually enrolled in stand-alone Part D plans throughout the study period were selected, which results in a slightly older population with higher percentage of female, non-white, diabetes and cardiovascular conditions.

4.6 Conclusion

Patterns of cardiovascular medication use are varied among elderly hypertensive patients who are newly diagnosed with CKD. Use of guideline-recommended ACEIs / ARBs is suboptimal among this population. Whether or not a patient receives therapies including ACEIs/ARBs is associated with patients' own demographic characteristics, co-existing conditions, as well as health plan benefits. Moreover, the present study indicates the significance of adding ACEIs /ARBs and statins to the anti-hypertensive regimens for hypertensive CKD patients. Findings of our study provide important information regarding the choice of medication.

Table 4-1 Descriptive statistics of individual demographic characteristics among elderly patients with hypertension and incident chronic kidney disease (CKD) by status of ACEIs/ARBs use (n=66,315)

Variable	ACEIs/ARBs user (n=32,973)*#	non-ACEIs/ARBs user (n=33,342)	All(n=66,315)
Baseline characteristics	*Mean(SD)/%*	*Mean(SD)/%*	*Mean(SD)/%*
Age (years)	78.3 (7.1)	80.3 (7.5)	79.4 (7.4)
<70	13.4	9.6	11.5
70-75	23.8	18.0	20.9
75-80	23.3	20.7	22.0
>80	39.5	51.7	45.7
Charlson comorbidity Index	1.0 (1.6)	1.3 (1.7)	1.2 (1.7)
Male	37.8	38.8	38.3
Race			
White	87.2	88.0	87.6
Black	9.4	9.0	9.2
Asians	1.6	1.5	1.6
Others	1.7	1.3	1.5
Unknown	0.1	0.1	0.1
Prescription coverage at baseline			
Part D without LIS	65.0	62.2	63.6
Part D with non-deemed LIS	2.2	2.0	2.1
Part D with deemed LIS	32.8	35.8	34.3
Diabetes mellitus (DM)	42.6	33.2	37.9
Follow-up characteristics			
Follow-up period (years)	5.0 (1.5)	3.9 (2.0)	4.5 (1.8)
Died	40.96	65.6	53.35
end-stage renal disease (ESRD)	1.1	0.9	1.0

ACEIs/ARBs use was defined as having at least one pharmacy claim of ACEIs/ARBs during a six-month period after the date of first diagnosis of CKD

* Continuously enrolled in Medicare A&B from 2006/1/1 and continuously enrolled in Medicare Part D from 2007 to end of 2013/date of death were required. A two-year baseline period was applied (2006-2007) to evaluate baseline characteristics, and a one-year baseline period (2007) was used to examine medication use history.

$ Adapted Charlson comorbidity index was calculated by excluding diabetes, kidney diseases and cardiovascular diseases

Table 4-2 Descriptive statistics of individual cardiovascular-related characteristics among elderly patients with hypertension and incident chronic kidney disease (CKD) by status of ACEIs/ARBs use (n=66,315)

Variable $	ACEIs/ARBs user (n=32,973)*#	non-ACEIs/ARBs user (n=33,342)	All(n=66,315)
Cardiovascular Comorbidities			
ASHD	45.3	44.3	44.8
AMI	9.6	9.0	9.3
CHF	26.7	28.7	27.7
CVA-TIA	27.3	29.6	28.5
PAD	31.6	35.6	33.6
AFIB	18.1	21.5	19.8
SCA/VA	4.7	4.6	4.6
Other Cardiovascular diseases	41.8	41.7	41.7
Cardiovascular Procedures			
PCI	3.2	2.4	2.8
CABG	0.9	0.7	0.8
ICD/CRT-D	0.6	0.5	0.5

#ACEIs/ARBs use was defined as having at least one pharmacy claim of ACEIs/ARBs during a six-month period after the date of first diagnosis of CKD

* Continuously enrolled in Medicare A&B from 2006/1/1 and continuously enrolled in Medicare Part D from 2007 to end of 2013/date of death were required. A two-year baseline period was applied (2006-2007) to evaluate baseline characteristics, and a one-year baseline period (2007) was used to examine medication use history.

$ Abbreviations: ASHD, atherosclerotic heart disease; AMI, acute myocardial infarction; CHF, congestive heart failure; CVA/TIA, cerebrovascular accident/transient ischemic attack; PAD, peripheral arterial disease; AFIB, atrial fibrillation; SCA/VA, sudden cardiac arrest and ventricular arrhythmias; PCI, percutaneous coronary interventions; CABG, coronary artery bypass grafting; ICD/CRT-D, implantable cardioverter defibrillators/cardiac resynchronization therapy with defibrillator devices.

Table 4-3 Descriptive statistics of individual medication-related characteristics among elderly patients with hypertension and incident Chronic Kidney Disease (CKD) by status of ACEIs/ARBs use (n=66,315)

Variable	ACEIs/ARBs user (n=32,973))# *	non-ACEIs/ARBs user (n=33,342)	All(n=66,315)
	Mean(SD)/%	*Mean(SD)/%*	*Mean(SD)/%*
N of Cardiovascular agents	2.5 (1.2)	0.8 (1.0)	1.6 (1.4)
Other anti-hypertension agents user $	80.8	48.1	64.3
Calcium channel blockers user	31.13	16.26	23.65
Beta-blockers user	53.23	33.05	43.08
Diuretics user	40.98	17.14	28.99
Statins user	54.34	27.93	41.06
Therapeutic strategies			
None	NA	44.63	22.44
Statins only	NA	7.31	3.67
Other Anti-hypertension agents only	NA	27.45	13.8
ACEIs/ARBs only	10.48	NA	5.21
Other Anti-hypertension agents+Statins	NA	20.62	10.37
ACEIs/ARBs+Statins	8.76	NA	4.36
ACEIs/ARBs +other anti-hypertension agents	35.18	NA	17.49
ACEIs/ARBs +other anti-hypertension agents+Statins	45.58	NA	22.66

Medication use was defined as having at least one pharmacy claim within each pharmacologic therapy during a six-month period after the date of first diagnosis of CKD

* Continuously enrolled in Medicare A&B from 2006/1/1 and continuously enrolled in Medicare Part D from 2007 to end of 2013/date of death were required. A two-year baseline period was applied (2006-2007) to evaluate baseline characteristics, and a one-year baseline period was used to examine medication use history.

& ACEIS/ARBs window is defined as time distance between first observed date of refilling ACEIs/ARBs and first observed date of CKD diagnosis.

$ Other anti-hypertension agents user defined as having any pharmacy claim of calcium channel blockers, beta-blockers or diuretics.

Table 4-4 The association between different pharmacologic therapies and developing end-stage renal disease (ESRD) among elderly patients with hypertension and incident chronic kidney disease (CKD) , using Cox proportional hazards (PH) model (n=66,315)

Variables&*$	HR	95% CI		
Therapeutic strategies #				
None	1.57	1.07	2.31	*
Statin only	0.67	0.38	1.19	
Other Anti-hypertension agents only	1.63	1.21	2.20	**
ACEIs/ARBs only	0.57	0.34	0.98	*
Statins+ other Anti-hypertension agents	ref	ref	ref	
Statins +ACEIs/ARBs	0.53	0.32	0.87	*
ACEIs/ARBs+ other Anti-hypertension agents	0.93	0.70	1.23	
Statins+ ACEIs/ARBs + other Anti-hypertension agents	0.69	0.52	0.92	*
N of drug classes received	1.17	1.06	1.29	**
Age (years)	0.95	0.94	0.96	***
Charlson comorbidity index	0.94	0.89	0.99	*
Male	1.33	1.14	1.57	***
Race (ref.White)				
Black	1.70	1.36	2.11	***
Asians	1.62	0.98	2.69	
Others	1.33	0.79	2.22	
Unknown	2.34	0.33	16.68	
Prescription coverage at baseline (Part D without LIS)				
Part D with non-deemed LIS	0.76	0.40	1.42	
Part D with deemed LIS	1.20	1.01	1.43	*
Diabetes mellitus (DM)	1.70	1.45	2.00	***
ASHD	0.88	0.73	1.06	
AMI	1.07	0.81	1.43	
CHF	1.30	1.07	1.58	**
CVA-TIA	0.87	0.72	1.04	
PAD	1.05	0.88	1.25	
AFIB	0.98	0.79	1.23	
SCA/VA	0.77	0.51	1.18	
Other Cardiovascular diseases	1.04	0.87	1.24	
PCI	0.73	0.44	1.22	
CABG	0.93	0.41	2.09	
ICD/CRT-D	0.74	0.23	2.38	

Medication use was defined as having at least one pharmacy claim within each pharmacologic therapy during a six-month period after the date of first diagnosis of CKD.

* Continuously enrolled in Medicare A&B from 2006/1/1 and continuously enrolled in Medicare Part D from 2007 to end of 2013/date of death were required. A two-year baseline period was applied (2006-2007) to evaluate baseline characteristics, and a one-year baseline period was used to examine medication use history.
$ patients were censored at the date of death or last CKD visits
Abbreviations: ASHD, atherosclerotic heart disease; AMI, acute myocardial infarction; CHF, congestive heart failure; CVA/TIA, cerebrovascular accident/transient ischemic attack; PAD, peripheral arterial disease; AFIB, atrial fibrillation; SCA/VA, sudden cardiac arrest and ventricular arrhythmias; PCI, percutaneous coronary interventions; CABG, coronary artery bypass grafting; ICD/CRT-D, implantable cardioverter defibrillators/cardiac resynchronization therapy with defibrillator devices.

Table 4-5 The association between different pharmacologic therapies and all-cause mortality among elderly patients with hypertension and incident chronic kidney disease (CKD), using Cox proportional hazards (PH) model (n=66,315)

Variables*	HR	95% CI		
Therapeutic strategies #$				
None	3.64	3.45	3.83	***
Statin only	1.05	0.98	1.13	
Other Anti-hypertension agents only	1.31	1.25	1.38	***
ACEIs/ARBs only	1.14	1.07	1.21	***
Statins+ other Anti-hypertension agents				
Statins +ACEIs/ARBs	0.85	0.79	0.91	***
ACEIs/ARBs+ other Anti-hypertension agents	1.08	1.03	1.13	***
Statins+ ACEIs/ARBs + other Anti-hypertension agents	0.88	0.84	0.93	***
N of drug classes received	0.94	0.92	0.95	***
Age (years)	1.05	1.05	1.05	***
Charlson comorbidity index	1.05	1.04	1.06	***
Male	0.98	0.96	1.00	
Race (White)				
Black	0.92	0.89	0.96	***
Asians	1.02	0.94	1.10	
Others	0.91	0.83	1.00	*
Unknown	0.83	0.63	1.10	
Prescription coverage at baseline (Part D without LIS)				
Part D with non-deemed LIS	1.25	1.17	1.34	***
Part D with deemed LIS	1.43	1.40	1.47	***
Diabetes mellitus (DM)	1.11	1.08	1.13	***
ASHD	1.06	1.04	1.09	**
AMI	1.09	1.05	1.13	***
CHF	1.29	1.26	1.32	***
CVA-TIA	1.06	1.03	1.08	***
PAD	1.08	1.05	1.10	***
AFIB	1.20	1.16	1.23	***
SCA/VA	1.05	0.99	1.10	
Other Cardiovascular diseases	0.96	0.94	0.98	***
PCI	0.91	0.85	0.98	**
CABG	0.73	0.64	0.84	***
ICD/CRT-D	1.13	0.98	1.29	

Continuously enrolled in Medicare A&B from 2006/1/1 and continuously enrolled in Medicare Part D from 2007 to end of 2013/date of death were required. A two-year baseline period was applied (2006-2007) to evaluate baseline characteristics, and a one-year baseline period was used to examine medication use history

* Medication use was defined as having at least one pharmacy claim within each pharmacologic therapy during a six-month period after the date of first diagnosis of CKD

Abbreviations: ASHD, atherosclerotic heart disease; AMI, acute myocardial infarction; CHF, congestive heart failure; CVA/TIA, cerebrovascular accident/transient ischemic attack; PAD, peripheral arterial disease; AFIB, atrial fibrillation; SCA/VA, sudden cardiac arrest and ventricular arrhythmias; PCI, percutaneous coronary interventions; CABG, coronary artery bypass grafting; ICD/CRT-D, implantable cardioverter defibrillators/cardiac resynchronization therapy with defibrillator devices.

Table 4-6 Predictors of ACEIs/ARBs use among elderly patients with hypertension and incident chronic kidney disease (CKD): multivariate logistic regression (n=66,315)

Variables#*$	OR	95% CI		
Age (years)	0.96	0.96	0.97	***
Charlson comorbidity index	0.91	0.90	0.92	***
Male	0.84	0.81	0.87	***
Race (White)				
Black	1.08	1.02	1.14	**
Asians	1.16	1.02	1.31	*
Others	1.23	1.08	1.40	**
Unknown	0.79	0.49	1.26	
Prescription coverage at baseline (Part D without LIS)				
Part D with non-deemed LIS	1.03	0.92	1.14	
Part D with deemed LIS	0.84	0.81	0.87	***
Diabetes mellitus (DM)	1.42	1.38	1.47	***
ASHD	1.10	1.06	1.15	***
AMI	1.04	0.98	1.10	
CHF	0.99	0.95	1.03	
CVA-TIA	0.96	0.92	0.99	*
PAD	0.91	0.88	0.94	***
AFIB	0.87	0.83	0.90	***
SCA/VA	1.04	0.96	1.13	
Other Cardiovascular diseases	1.09	1.06	1.13	***
PCI	1.18	1.07	1.30	**
CABG	1.04	0.87	1.24	
ICD/CRT-D	1.08	0.87	1.35	

#ACEIs/ARBs use was defined as having at least one pharmacy claim of ACEIs/ARBs during a six-month period after the date of first diagnosis of CKD

* Continuously enrolled in Medicare A&B from 2006/1/1 and continuously enrolled in Medicare Part D from 2007 to end of 2013/date of death were required. A two-year baseline period was applied (2006-2007) to evaluate baseline characteristics, and a one-year baseline period was used to examine medication use history.

$ Anti-hypertension agents user defined as having any pharmacy claim of calcium channel blockers, beta-blockers or diuretics.

Abbreviations: ASHD, atherosclerotic heart disease; AMI, acute myocardial infarction; CHF, congestive heart failure; CVA/TIA, cerebrovascular accident/transient ischemic attack; PAD, peripheral arterial disease; AFIB, atrial fibrillation; SCA/VA, sudden cardiac arrest and ventricular arrhythmias; PCI, percutaneous coronary interventions; CABG, coronary artery bypass grafting; ICD/CRT-D, implantable cardioverter defibrillators/cardiac resynchronization therapy with defibrillator devices.

Table 4-7 Sensitivity analysis: the association between different pharmacologic therapies and developing end-stage renal disease (ESRD) among elderly patients with hypertension and incident chronic kidney disease (CKD) , using Cox proportional hazards (PH) model (n=66,315)

Variables&*	HR	95% CI		
Therapeutic strategies				
None	2.75	1.87	4.05	***
Statin only	1.05	0.67	1.64	
Other Anti-hypertension agents only	1.93	1.42	2.61	***
ACEIs/ARBs only	1.17	0.78	1.75	
Statins+ other Anti-hypertension agents	Ref	Ref	Ref	
Statins +ACEIs/ARBs	0.88	0.56	1.40	
ACEIs/ARBs+ other Anti-hypertension agents	1.01	0.74	1.37	
Statins+ ACEIs/ARBs + other Anti-hypertension agents	0.58	0.42	0.82	**

* Demographics and clinical factors were adjusted.

Table 4-8 Sensitivity analysis: the association between different pharmacologic therapies and all-cause mortality among elderly patients with hypertension and incident chronic kidney disease (CKD) , using Cox proportional hazards (PH) model (n=66,315).

Variables*	HR	95% CI		
Therapeutic strategies				
None	4.92	4.63	5.23	***
Statin only	1.59	1.49	1.70	***
Other Anti-hypertension agents only	1.54	1.46	1.63	***
ACEIs/ARBs only	1.67	1.57	1.77	***
Statins+ other Anti-hypertension agents	Ref	Ref	Ref	
Statins +ACEIs/ARBs	0.93	0.86	1.01	
ACEIs/ARBs+ other Anti-hypertension agents	1.04	0.98	1.10	
Statins+ ACEIs/ARBs + other Anti-hypertension agents	0.78	0.74	0.83	***

* Demographics and clinical factors were adjusted.

Chapter 5

DISSERTATION MANUSCRIPT TWO: Effects of adherence to angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers inhibitors (ARBs) on the progression of chronic kidney disease (CKD) in Medicare Part D enrollee

5.1 Abstract

OBJECTIVES Limited research has systematically assessed the long-term effects of adherence to ACEIs and ARBs in delaying the progression of CKD and death using large patient cohorts. This study examined how patients' ACEIs and ARBs utilization potentially related with renal failure and mortality among hypertensive Medicare Part D-enrolled CKD patients in the United States.

METHODS This retrospective cohort study was conducted using Medicare 5% sample claim data from USRDS (2006-2013). Elderly Medicare beneficiaries who were diagnosed with hypertension and CKD, having a history of using ACEIs/ARBs, and continuously enrolled in Medicare Part D were included. Baseline characteristics were examined using a two year baseline period. Adherence to ACEIs, ARBs and other blood pressure/ lipid lowering agents was measured as time-dependent covariates using Proportion of Days Covered (PDC). The time-dependent Cox proportional hazard regression was performed to estimate the relationship between medication adherence and progression to end-stage renal disease (ESRD) and death.

RESULTS A total of 65,574 hypertensive CKD patients were included. Approximately 2.7% of them developed ESRD and 54.9% of them died during the follow-up period. Consistently being adherent to ACEIs and ARBs was associated with a significant decreased hazard of developing ESRD (Hazard Ratio: 0.11 95%CI [0.11–0.12] p<0.0001; 0.11 95% CI [0.10, 0.12]; p<0.0001) after adjusting for demographic and clinical confounders. Patients with good adherence to ACEIs and ARBs throughout study period had a reduced risk of death (Hazard Ratio: 0.10 95%CI [0.10–0.11] p<0.0001; 0.10 95% CI [0.09, 0.10]; p<0.0001). Increased adherence to calcium channel blockers, beta-blockers, diuretics, and statins was associated with lower ESRD and mortality risk.

CONCLUSIONS Increased adherence to ACEIs and ARBs, as well as other cardiovascular agents, for elderly patients with hypertension and CKD is associated with delay in CKD progression and lower mortality risk. These findings could have important implications for hypertension management in this population.

5.2 Introduction

CKD is becoming a serious public health issue worldwide because of the growing prevalence of CKD and the rising burden from CKD and its serious complications[13,174]. In United State, the prevalence of recognized CKD in Medicare beneficiaries increased to 15% in 2014. The total Medicare expenditures on CKD reached $52.8 billion in 2014—about 21% of total Medicare expenditures [1]. Additionally, healthcare expenditures on CKD are increased with disease progression. CKD patients who progressed to renal failure, also called ESRD, need to receive costly kidney replacement therapy, either regular dialysis or kidney transplantation, to stay alive. As reported by the USRDS ADR, the average per person per year Medicare spending for ESRD patients was 3.3 times greater than CKD patients, at $75,214, compared to $22,745 in 2014. Patients with advanced CKD were more likely to experience adverse cardiovascular outcomes[22]. In fact, a majority of CKD patients died prior the occurrence of ESRD[56,175]. Thus, delaying the progression of CKD and reducing CKD related mortality have significant meaning for reducing financial burden on the healthcare system, as well as improving individual utility and social welfare.

Oral medications, particularly anti-hypertension agents, play a significant role in CKD treatment. Findings from nationally representative data illustrated that nearly 74% of elderly CKD patients in the United States had hypertension[1]. In addition, uncontrolled blood pressure is the second leading cause of kidney failure (diabetes is the lead cause) in the United States[39]. Previous studies found patients with uncontrolled blood pressure had a more rapid rate of CKD progression[176,177]. Although anti-hypertension agents and statins were widely used in CKD patients, as these medications occupied 3 of 5 most commonly used oral medications in elderly CKD patients, the prevalence of uncontrolled blood pressure remained

high[1,86,166]. This may attributable to the suboptimal compliance with the prescribed anti-hypertension treatment[4,88,120].

ACEIs and ARBs are recommended to CKD patients by clinical practice guidelines, particular for patients whose underlying cause of CKD was diabetes, as well as hypertensive patients with mild kidney dysfunctions[42,94]. Findings derived from clinical research provided evidence that ACEIs and ARBs had renoprotective effects for CKD patients in addition to lowering blood pressure[6,95,96,178]. However, there was lack of real world evidence from observational studies to support the long-term use of these two drug classes. Previous observational studies had assessed the effects of adherence with prescribed anti-hypertension treatment in CKD patients, but they were limited by small sample size and self-reported measurements of medication taking behaviors[120]. Most importantly, these studies did not have a sufficiently long observation periods to examine the long-term survival benefit of being adherent to anti-hypertension treatment, such as delaying progression to ESRD and lowering risk of mortality. In this study, we proposed to assess the association between ACEIs/ARBs adherence and CKD outcomes in hypertensive CKD patients using a retrospective cohort design with long-term follow-up. Additionally, current research literature found CKD patients generally had a heavy pill burn and a majority of them received multiple anti-hypertension agents to regulate their blood pressure[4,88,91,92]. We therefore developed time-dependent measurements of medication adherence for not only ACEIs and ARBs, but also the other four drug classes that had been widely used in CKD patients: statins, diuretics, beta-blockers, and calcium channel blockers. The time-varying measurement of medication adherence helped us to precisely capture the discontinuation and change (switching or adding on) that might occur in CKD treatments.

5.3 Methods

5.3.1 Study design and data source

This observational study developed a retrospective cohort of elderly hypertensive CKD patients in the United States, using data on the 5% Medicare cohort from the USRDS database (2006-2013). The 5% sample of Medicare claims are linked to the USRDS ESRD database, which contain information on initiation of ESRD extracted from the Medical Evidence form (CMS2728) and information on all-cause death obtained from the ESRD Death Notification form (CMS 2746) and the Master Beneficiary Summary File.

This study design comprised three main periods. A selection period starting from January 1, 2006 to December 31, 2012 was assigned to select hypertensive patients who had a diagnosis of CKD. All study subjects were then followed from the index date, January 1, 2008, until the date of death or the end of the study, December 31, 2013. A 2-year and 1-year baseline period prior to the index date were employed to assess comorbidity history and medication use history separately.

5.3.2 Study population

Patients were included if they had a diagnosis of CKD during the selection period and had be diagnosed with hypertension prior to the index date. We employed a previously validated method: having at least one inpatient claim or two outpatient claims to identify patients with hypertensive CKD. In order to capture all Medicare claims for our study subjects, we further restricted the study cohort to elderly subjects who continuously enrolled in Medicare Part A&B and covered by stand-alone Part D plans. To ensure our study subjects had a

sufficiently long follow-up period, exclusion in the cohort required the date of first observed CKD related claim was later than January 1, 2013, developing ESRD before the index date and having non CKD related claim in the follow-up period. Lastly, we excluded patients without any pharmacy claim of ACEIs/ARBs at baseline. Having a history of using ACEIs/ARBs might indicate that ACEIs/ARBs were applicable to these patients.

5.3.3 Measures

Survival outcome measures

ESRD free time was set as the time from the index date to the date of first ESRD service reported by the CMS 2728 form. Patients without presence of ESRD by the end of our study were censored at the date of death or the date of the last CKD related visit. Overall survival time referred to the time between the index date and the date of death from all-cause.

Medication adherence

We developed time-varying repeated measures to assess patients' adherence to their prescribed ACEIs and ARBs. PDC was established as a proffered method to evaluate medication adherence[179]. Thus, a three-month PDC was calculated quarterly for each drug class from the index date until the date of death or the end of the study. For each specified drug class, we first aggregated total days of supply over a three-month window, and then subtracted the overlap days and divided by 90 days. We used PDC threshold of 80% to distinguished patients who had good adherence and those who had poor adherence. A time-dependent dummy variable of medication adherence was further developed, where 1 indicated PDC above 80%. A one-year fixed PDC in the baseline period and an overall PDC in the follow-up period were assessed by the same algorithmic structure.

Covariate measures

The following covariates were adjusted when we examined the association between medication adherence and CKD related outcomes including demographic variables (age, gender, race), Part D coverage, and comorbid conditions. Age was calculated at the index date. In term of Part D coverage, patients were first stratified into with and without LIS groups based on whether or not had at least one month of low income subsidy at baseline. We then separated patients with deemed LIS from patients with non-deemed LIS. Different with those without LIS, Part D enrollees with LIS were not limited by the gap in prescription drug coverage, also known as "donut hole". And deemed LIS beneficiaries typically have the lowest premiums and copayments compared to the other two groups[151]. Comorbid conditions at baseline were evaluated using the same algorithmic structure as described in study design. Separate indictors were generated for conditions that closely related with CKD, like diabetes, cardiovascular conditions and procedures. Meanwhile, adapted Charlson comorbidity index was calculated to measure the overall comorbidity burden. Moreover, medication use of other commonly used cardiovascular agents like beta-blockers, calcium channel blockers, diuretics and statins were evaluated using PDC.

5.3.4 Statistical analyses

Descriptive analyses of demographics, medical history, and medication use related characteristics were conducted using means for continuous variables and percentages of categorical variables. The Multivariate Cox proportional hazards regression analyses with medication adherence as time-varying covariates were performed to assess the association between adherence to ACEIs/ARBs and progression to ESRD and all-cause mortality.

5.4 Results

We studied a total of 65,574 elderly Medicare beneficiaries with hypertensive and CKD who had taken at least one medication of ACEIs/ARBs in the baseline period. The study subjects were followed on average of 4.3 years (table 5-1). Nearly half (54.9%) of them died by the end of this study, while only 2.7% of them had presence of ESRD. More than half of patients were aged above 75 with a mean age of 79.2 years; 39.3% were male; and 86.4% were white, 10.1% were black and 1.8% were Asian-American. In addition, about half of patient had been diagnosed with diabetes (47.5%) and the mean Charlson comorbidity score was 1.4 for this population. Table 5-2 described patients' cardiovascular related conditions and procedures at baseline and follow-up period. Approximately half of patients had diagnosis of ASHD at baseline (52.8%), and about one-third of them had onset of CHF, CVA-TIA and PAD (37.8%, 32.9%, and 40.8% respectively). The percentage of patients received PCI was three times greater than those received coronary artery bypass grafting (CABG), an alternative intervention of PCI (4.1% versus 1.4%). An increased prevalent was observed in all cardiovascular conditions and procedures from baseline to follow-up.

Table 5-3 presented utilization of investigated drug classes in our study cohort. With regard to utilization rate of each drug class at baseline, about two-third of our study subjects had used at least one medication of ACEIs and this prevalence was 40% for ARBs. The other four drug classes were widely used in this population as well, as about half of our population had ever used statins, beta-blockers, and diuretics, and one-third of them had ever used calcium channel blockers at baseline. Additionally, the utilization rate of the investigated drug classes were all increased from baseline to follow-up, varied from 8% for ARBs to 60% for calcium

channel blockers. In term of medication adherence at baseline, measured as the proportion of days covered by the specified drug class in the year of 2007, 63.1% and 61.8% of our study subjects were adherent to their prescribed ACEIs and ARBs respectively (PDC above 80%). Meanwhile, more patients were qualified for being adherent to statins and diuretics (59.6% and 61.3%) than those qualified for being adherent to beta-blockers and calcium channel blockers (50.4% and 56.6%). When we assessed the medication adherence in long run, adherence rate decreased sharply in all of the six studied drug classes.

Table 5-4 reported the association between medication adherence and progression with adjustment of demographic and clinical history covariates. Hypertensive CKD patients with consistently good adherence of ACEIs had an 89% lower risk of developing ESRD (HR=0.11, $p<0.0001$) compared to those with consistently poor adherence. Consistently adherent to ARBs was also associated with a significantly decreased risk of ESRD (HR=0.11, $p<0.0001$). Risk factors of ESRD included older age, white race, greater comorbidity burden, receiving any type of Part D low-income-subsidy, onset of diabetes and cardiovascular conditions. It was worth to note that patients who received PCI and CABG had a lower risk of ESRD (HR=0.90, p=0.0001 and HR=0.75, $p<0.0001$, respectively), while patients who received cardiac resynchronisation therapy like implantable cardioverter defibrillators (ICD)/cardiac resynchronization therapy with defibrillator devices (CRT-D) were more likely to develop ESRD (HR=1.16, p=0.0024). As expected, being adherence to other cardiovascular agents besides ACEIs/ARBs was associated with a substantial decreased risk of ESRD as well.

Results of time-dependent Cox proportional hazard regression of all-cause mortality were showed in table 5-5. Being adherent to ACEIs and ARBs throughout the follow-up period were associated a 90% decreased in risk of death (both HR=0.10, p<0.0001). The same risk factors and protective factors of death were identified as in the model of ESRD. Patients who were older, white, receiving subsidy for their Part D coverage, having onset of diabetes and cardiovascular conditions were more likely to die in the study period. Additionally, receiving cardiovascular intervention PCI and CABG were significantly related with a lower risk of mortality (HR=0.91, p=0.0003, and HR=0.75, p<0.0001), but not ICD/CRT-D (HR=1.16, p=0.0025). Meanwhile, continuously being good adherent to statins and other anti-hypertension agents were associated with significantly lowering risk of death.

5.5 Discussion

To the best of our knowledge, this study is the first observational study to assess the long-time benefits of adherence with ACEIs and ARBs in elderly patients with hypertension and CKD. A strength of this study is that hypertensive CKD patients were extracted from a nationally representative database, and they were followed up to 6 years to observe CKD outcomes. Moreover, by employing the time-varying measures of medication adherence, we were able to take both changes (either switching or adding on) and discontinuation of regimens into account when examined the relationship between medication use and treatment outcome.

As observed in previous cohort studies, CKD patients were more likely to die before progression to ESRD[22,180]. The mortality rate was higher in our study population, which may because we had an older cohort with an average age of 79.2 years and high prevalence of

cardiovascular conditions. As expected, utilization rate of investigated cardiovascular agents were increased from baseline to follow-up, and calcium channel blocker demonstrated the highest increasing rate (60%), followed by beta-blockers (48%), diuretics (28%) and statins (26%). These changes may due to the long observation time in follow-up period and the changes in pharmacological therapies. Anti-hypertension treatment regimen is individualized based on demographics, onset of comorbid conditions, therapeutic goal, efficacy, tolerability and cost[181]. For example, physicians may need to add a new drug when patients cannot achieve the target blood pressure with the current anti-hypertension treatment regimen. In another case, patients may initiate ACEIs/ARBs after being diagnosed with diabetes.

In term of medication adherence, our study demonstrated a slightly lower adherence rate (50%-60%) compared to previous research (65%-70%) because of the different measurements and study population characteristics[122]. In addition, we found adherence rate decreased to 27%-46% in the follow-up period. A study by Chang et al followed a cohort of patients who were discharged from hospital for myocardial infarction. Researchers found patients' adherence to prescribed ACEIs/ARBs, beta-blockers and statins were all decreased over the three-year study period. And patients with worse kidney function at baseline had a lower long-term medication adherence[123]. Another study of 140 CKD patients by Magaho et al found patients' adherence to medication varied over time[121]. Medication adherence was assessed in person at baseline and by phone interview at 12-month follow-up. Patients were considered as adherence if they were able to correctly report all medications that they were prescribed and take their medications on time without skipping doses. Researchers found the adherence rate increased from 17.4% at baseline to 26.8% at follow-up. Moreover, about 50% of adherent patients became non-adherent and 22% of non-adherent patients turned to be

adherent at follow-up. Overall, the changes in regimens and medication adherence emphasize the significance of developing time-varying measurements for medication adherence.

Results of our survival analyses showed that hypertensive CKD patients with consistently good adherence to ACEIs and ARBs had a substantial decreased risk of developing ESRD and mortality, after adjusting for demographic, clinical and medication use confounders. In order words, regardless patients' utilization of other cardiovascular agents, consistently being adherent to ACEIs/ARBs had independent protective effects on delaying renal dysfunctions and extending the overall survival. Our findings were consistent with evidence derived from randomized controlled trials[94]. A study by Yasuda evaluated the effects of adding ARBs to conventional therapy (without ARBs) on CKD progression and found patients who received therapy including ARBs had a 42.5% decreased risk of renal event[178]. We also found onset of cardiovascular conditions at baseline was associated with increased risk of ESRD and mortality. This may because cardiac dysfunction may worsen kidney function through several mechanisms, such as haemodynamic abnormalities, neurohormonal activation, and inflammatory activation[53].

There are some limitations in this study. First, external validity was threatened by our study design, that is, aged Medicare beneficiaries with CKD and hypertension who were covered by stand-alone Part D plans and having a history of ACEIs/ARBs use were selected in this study. Meanwhile, restrict inclusion criteria in this study may result in selection bias. By requiring of continuously enrolled in Medicare Part D throughout the study period, we obtained a study cohort that was slightly older, having more women, non-white, and having a heavier burden of illness. Second, the precision of medication use measures was limited by

the characteristics of pharmacy claims data. Patients with multiple prescription drug coverage may get ACEIs/ARBs through the program other than Part D. That resulted in underestimates of time-varying PDC in this study. Meanwhile, by using pharmacy claims data, we assume the dispensed drug was actually taken by the patient, which results in overestimates of our medication use. Overall, imprecise measures of medication adherence may bias our results to any direction. Third, patients with better medication adherence may indicate they visit primary physicians/ nephrologists more frequently, which could in turn allow physicians have more chances to detect their renal events earlier compared with those who visit physicians fewer times per year. In this case, the effect of ACEIs and ARBs were overestimated. This study may also suffer from omitted variable bias. Confounder variables like hospitalization and control of blood pressure were not adjusted in this study. For further analyses, we would improve our model by adding time-varying measurement of hospitalization. Meanwhile, we would assess the long-term benefits of using ACEIs/ARBs on cardiovascular events. Further researchers were also recommended to assess the long-term effects of ACEIs/ARBs on CKD progression if laboratory measures were available, such as halving of estimated GFR or doubling of serum creatinine.

5.6 Conclusion

In summary, medication adherence to ACEIs and ARBs was suboptimal in elderly patients with hypertension and CKD. Moreover, the adherence rates were decreased over time. Our study found increasing adherence to ACEIs or ARBs, as well as other cardiovascular agents, for patients diagnosed with both CKD and hypertension could substantially delaying their occurrence of ESRD and mortality. The findings of our study provided important information on physicians' prescribing strategies aimed at preventing CKD progression and improving treatment outcomes among aged hypertensive patients with CKD.

Table 5-1 Descriptive statistics of individual demographic characteristics among elderly patients with hypertension and chronic kidney disease (CKD) (n=65,574)

*Baseline characteristics**	*Mean (SD)/%*
Age (years)	79.2 (7.3)
Age (years)	
<70	11.9
70-75	21.2
75-80	22.5
>80	44.5
Male	39.3
Race	
White	86.4
Black	10.1
Asians	1.8
Others	1.6
Unknown	0.1
Prescription coverage at baseline	
Part D without LIS	61.3
Part D with non-deemed LIS	2.2
Part D with deemed LIS	36.5
Diabetes mellitus (DM)	47.5
Charlson comorbidity index$	1.4 (1.8)
Follow-up characteristics	
Follow-up period (years)	4.3 (2.0)
Died	54.9
End-stage renal disease (ESRD)	2.7

* Continuously enrolled in Medicare A&B from 2006/1/1 and continuously enrolled in Medicare Part D across the follow-up period (2008-2013)/date of death were required. A two-year baseline period was applied (2006-2007) to evaluate medical history, and a one-year baseline period (2007) was used to examine medication use history. CKD patients with date of last CKD claim before 01/01/2008 and CKD patients with date of first CKD claim after 01/01/2013 are excluded. CKD patients with ESRD diagnosis before 01/01/2008 were excluded. Patients without any use of ACEIs/ARBs in baseline period were excluded.

$ Adapted Charlson comorbidity index was calculated by excluding diabetes, kidney diseases and cardiovascular diseases

Table 5-2 Descriptive statistics of individual cardiovascular-related characteristics among elderly patients with hypertension and chronic kidney disease (CKD) (n=65,574)

Variables$	Baseline (2006-2007, %)*	Follow-up (2008-2013, %)
Cardiovascular Comorbidities		
ASHD	52.8	72.3
AMI	13.7	31.1
CHF	37.8	64.6
CVA-TIA	32.9	56.5
PAD	40.8	73.1
AFIB	23.7	45.6
SCA/VA	6.5	19.7
Other Cardiovascular diseases	49.1	74.9
Cardiovascular Procedures		
PCI	4.1	9.5
CABG	1.4	3.7
ICD/CRT-D	1.1	2.5

* Continuously enrolled in Medicare A&B from 2006/1/1 and continuously enrolled in Medicare Part D across the follow-up period (2008-2013)/date of death were required. A two-year baseline period was applied (2006-2007) to evaluate medical history, and a one-year baseline period (2007) was used to examine medication use history. CKD patients with date of last CKD claim before 01/01/2008 and CKD patients with date of first CKD claim after 01/01/2013 were excluded. CKD patients with ESRD diagnosis before 01/01/2008 were excluded.
$ Abbreviations: ASHD, atherosclerotic heart disease; AMI, acute myocardial infarction; CHF, congestive heart failure; CVA/TIA, cerebrovascular accident/transient ischemic attack; PAD, peripheral arterial disease; AFIB, atrial fibrillation; SCA/VA, sudden cardiac arrest and ventricular arrhythmias; PCI, percutaneous coronary interventions; CABG, coronary artery bypass grafting; ICD/CRT-D, implantable cardioverter defibrillators/cardiac resynchronization therapy with defibrillator devices.

Table 5-3 Descriptive statistics of individual medication-related characteristics among elderly patients with hypertension and chronic kidney disease (CKD) (n=65,574)

Variables	Baseline (2007, %)*	Follow-up (2008-2013, %)
Medication Use#		
ACEIs	67.0	68.1
ARBs	40.5	43.9
Statins	53.1	66.9
Calcium channel blockers	30.9	49.4
Beta-blockers	46.3	68.7
Diuretics	45.4	57.9
Medication Adherence (PDC above 80%) $		
ACEIs	63.1	36.8
ARBs	61.8	36.7
Statins	59.6	42.1
Calcium channel blockers	61.3	36.9
Beta-blockers	50.4	45.8
Diuretics	56.6	26.8

* Continuously enrolled in Medicare A&B from 2006/1/1 and continuously enrolled in Medicare Part D across the follow-up period (2008-2013)/date of death were required. A two-year baseline period was applied (2006-2007) to evaluate medical history, and a one-year baseline period (2007) was used to examine medication use history. CKD patients with date of last CKD claim before 01/01/2008 and CKD patients with date of first CKD claim after 01/01/2013 were excluded. CKD patients with ESRD diagnosis before 01/01/2008 were excluded.

Medication use was defined as having any pharmacy claim within each drug class

$ PDC was calculated as proportion of days covered by the specific drug class. PDC above 80% was classified as having good adherence

Table 5-4 The association between medication adherence and developing end-stage renal disease (ESRD) among elderly patients with hypertension and chronic kidney disease (CKD) , using time-dependent Cox proportional hazards (PH) model (n=65,574)

Variables*	Hazard Ratio	95% Confidence Interval		
Age (years)	1.04	1.04	1.04	***
Charlson comorbidity index$	1.04	1.04	1.05	***
Gender				
Female	ref	ref	ref	
Male	0.95	0.93	0.97	***
Race				
White	ref	ref	ref	
Black	0.92	0.89	0.95	***
Asians	1	0.92	1.07	
Others	0.85	0.78	0.92	***
Unknown	1	0.78	1.28	
Part D coverage				
without LIS	ref	ref	ref	
with non-deemed LIS	1.32	1.24	1.42	***
with deemed LIS	1.45	1.42	1.48	***
Diabetes mellitus (DM)	1.24	1.21	1.26	***
Baseline Cardiovascular diseases/procedures$				
ASHD	1.12	1.10	1.15	***
AMI	1.14	1.10	1.17	***
CHF	1.40	1.36	1.43	***
CVA-TIA	1.02	0.99	1.04	
PAD	1.13	1.10	1.15	***
AFIB	1.18	1.15	1.21	***
SCA/VA	1.09	1.04	1.13	***
Other Cardiovascular diseases	0.99	0.97	1.01	
PCI	0.93	0.88	0.98	***
CABG	0.76	0.69	0.83	***
ICD/CRT-D	1.19	1.08	1.31	**
Time-dependent Medication Adherence (PDC above 80%)#				
ACEIs	0.17	0.17	0.18	***
ARBs	0.16	0.16	0.17	***
Statins	0.27	0.26	0.28	***
Calcium channel blockers	0.39	0.38	0.40	***
Beta-blockers	0.36	0.35	0.37	***
Diuretics	0.41	0.40	0.43	***

* Continuously enrolled in Medicare A&B from 2006/1/1 and continuously enrolled in Medicare Part D across the follow-up period (2008-2013)/date of death were required. A two-year baseline period was applied (2006-2007) to evaluate medical history, and a one-year baseline period (2007) was used to examine medication use history. CKD patients with date of last CKD claim before 01/01/2008 and CKD patients with date of first CKD claim after 01/01/2013 were excluded. CKD patients with ESRD diagnosis before 01/01/2008 were excluded.

$ Abbreviations: ASHD, atherosclerotic heart disease; AMI, acute myocardial infarction; CHF, congestive heart failure; CVA/TIA, cerebrovascular accident/transient ischemic attack; PAD, peripheral arterial disease; AFIB, atrial fibrillation; SCA/VA, sudden cardiac arrest and ventricular arrhythmias; PCI, percutaneous coronary interventions; CABG, coronary artery bypass grafting; ICD/CRT-D, implantable cardioverter defibrillators/cardiac resynchronization therapy with defibrillator devices

Medication adherence for each drug class was measured quarterly, and a dummy variable was developed, where 1 indicated PDC above 80%

Table 5-5 The association between medication adherence and all-cause mortality among elderly patients with hypertension and chronic kidney disease (CKD), using time-dependent Cox proportional hazards (PH) model (n==65,574)

Variables*	Hazard Ratio	95% Confidence Interval		
Age (years)	1.05	1.04	1.05	***
Baseline Charlson comorbidity index	1.04	1.04	1.05	***
Gender				
Female	ref	ref	ref	
Male	0.94	0.92	0.96	***
Race				
White	ref	ref	ref	
Black	0.88	0.85	0.91	***
Asians	0.97	0.90	1.05	
Others	0.81	0.75	0.89	***
Unknown	0.96	0.75	1.24	
Part D coverage				
without LIS	ref	ref	ref	
with non-deemed LIS	1.33	1.25	1.43	***
with deemed LIS	1.46	1.43	1.50	***
Diabetes mellitus (DM)	1.22	1.19	1.24	***
Baseline Cardiovascular diseases/procedures$				
ASHD	1.13	1.10	1.16	***
AMI	1.14	1.10	1.17	***
CHF	1.38	1.34	1.41	***
CVA-TIA	1.02	1.00	1.05	
PAD	1.12	1.10	1.15	***
AFIB	1.19	1.16	1.22	***
SCA/VA	1.10	1.05	1.14	***
Other Cardiovascular diseases	0.99	0.96	1.01	
PCI	0.94	0.89	0.99	*
CABG	0.75	0.68	0.83	***
ICD/CRT-D	1.18	1.07	1.30	***
Time-dependent Medication Adherence (PDC above 80%)#				
ACEIs	0.17	0.17	0.18	***
ARBs	0.15	0.15	0.16	***
Statins	0.25	0.24	0.25	***
Calcium channel blockers	0.33	0.32	0.35	***
Beta-blockers	0.33	0.32	0.34	***
Diuretics	0.39	0.38	0.41	***

* Continuously enrolled in Medicare A&B from 2006/1/1 and continuously enrolled in Medicare Part D across the follow-up period (2008-2013)/date of death were required. A two-year baseline period was applied (2006-2007) to evaluate medical history, and a one-year baseline period (2007) was used to examine medication use history. CKD patients with date of last CKD claim before 01/01/2008 and CKD patients with date of first CKD claim after 01/01/2013 are excluded. CKD patients with ESRD diagnosis before 01/01/2008 are excluded.

$ Abbreviations: ASHD, atherosclerotic heart disease; AMI, acute myocardial infarction; CHF, congestive heart failure; CVA/TIA, cerebrovascular accident/transient ischemic attack; PAD, peripheral arterial disease; AFIB, atrial fibrillation; SCA/VA, sudden cardiac arrest and ventricular arrhythmias; PCI, percutaneous coronary interventions; CABG, coronary artery bypass grafting; ICD/CRT-D, implantable cardioverter defibrillators/cardiac resynchronization therapy with defibrillator devices.
# Medication adherence for each drug class was measured quarterly, and a dummy variable was developed, where 1 indicated PDC above 80%

Chapter 6

DISSERTATION MANUSCRIPT THREE: Environmental and individual predictors of medication adherence among elderly patients with hypertension and chronic kidney disease (CKD): a geospatial approach

6.1 Abstract

OBJECTIVES: Previous research in the elderly has shown medication cost, regimen complexity, health literacy, and cognitive function to be associated with medication adherence. Few studies have assessed geographical variation in medication adherence across different regions. This study aimed to explore local variation in medication adherence and examine environmental and individual influences on adherence to angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) among elderly hypertensive CKD patients in the United States.

METHODS: This retrospective cohort study utilized a linked dataset from Medicare 5% sample claim data (2006-2013), American Community Survey 5-Year Data (2005-2009) and the Health Resources and Services Administration (HRSA) Primary Care Service Area (PCSA) data (2007). We included hypertensive CKD patients who were aged 67 and above, continuously enrolled in Medicare Part D and had at least one ACEIs/ARBs pharmacy claim. Patients' one-year adherence to ACEIs/ARBs was measured using Proportion of Days Covered (PDC), and then aggregated as a mean PDC at county level. Contextual factors including rate

of general physician (per 10,000), proportion of population residing in MUAs and deprivation score were derived for each county. The geographically weighted regression (GWR) and the linear mixed-effects models were applied to investigate the relationship between environmental, individual risk factors and medication adherence.

RESULTS: A total of 70,201 eligible patients with hypertension and chronic kidney disease residing in 2,981 counties of the United States using ACEIs/ARBs were included in the final sample. The mean ACEIs/ARBs PDC by county was 0.76±0.12 SDs. Significant spatial autocorrelation was observed in average ACEIs/ARBs PDC, as the West North Central and New England region had higher average adherence rate compared with the East South Central and West South Central regions. The GWR model demonstrated significant improvement relative to the global regression model. Proportion of population residing in MUAs and deprivation score were related with lower average PDC. Results of the linear mixed-effect model highlighted several individual statistically significant ($p<0.05$) risk factors for non-adherence including higher comorbidity severity score, and having multiple cardiovascular diseases. Patients, who were female, white, enrolled in Part D Low-income Subsidy program, having diabetes and atrial fibrillation were associated with better adherence.

CONCLUSIONS: Medication adherence is geographically differentiated across the United States. Both contextual and individual factors such as proportion of population residing in MUAs, county deprivation score, and coverage of Part D Low-income Subsidy program are factors that are related with medication adherence. Such factors may be helpful in the design of local interventions focused on improving patient outcomes, from a population perspective.

6.2 Introduction

ACEIs and ARBs are recommended by the practice guideline as preferred anti-hypertension agents for CKD patients because of their additional renoprotective benefits[42,94]. Compliance to anti-hypertensive treatment is crucial for patients with hypertensive CKD, as poor medication adherence may result in uncontrolled blood pressure, and further accelerate the rate of CKD progression and increase risk of hospitalization, cardiovascular conditions and death[4,88,120,163]. A previous research using nationally representatively data showed approximately only one-third of CKD patients in the United States had their blood pressured under controlled[86]. Despite the importance of anti-hypertensive agents, adherence to anti-hypertensive agents remains suboptimal in this population. Previous studies of medication compliance found approximately 65% - 83% of CKD patients had good adherence to their prescribed anti-hypertensive agents, while studies using self-report measures of adherence generally demonstrated a better adherence rate than those using objective measures (67%-83% versus 65%-70%)[4,88,120–122].

Reasons of having poor adherence to anti-hypertensive treatment in CKD patients may be different from study to study because of the distinct characteristics of investigated medications and populations. For example, individuals' social and demographic factors like younger age, male, lower level of income and education were associated with increased risk of poor adherence in some studies but not in others[88,120,121,131].Regarding to patients' health status, patients with depression, having more hospitalizations, and unable to self-administrate their medications were more likely to have poor medication compliance[4,88,121]. Inconsistent relationship between mediation adherence and renal function were observed in previous research[4,123,131]. Moreover, interview based and survey based studies found that forgetfulness

was the most common reason of nonadherence reported by CKD patients[88,120,132]. Compliance to anti-hypertension treatments in CKD patients were also influenced by other subjective factors, like patients' perceived need of mediations, perceived efficacy of medication, concerns of side effects, as well as physician-patient communications[132,133]. With regard to characteristics of treatment, side effect, complexity of regimens and the overall pill burden were established risk factors of poor medication adherence[121,134].

Although a number of studies have explored predictors of poor adherence to medications, few of them have examined how medication adherence varied across different regions, in addition, how neighborhood-level factors were related with individuals' medication taking behaviors. One recently published medication adherence study by Erickson et al found there was a geographical clustering in adherence to statins in the state of Michigan[182]. Similarly, another study by Hoang et al observed a spatial clustering in medication adherence when they followed a total of 1081 patients residing in the southeast of Michigan State who were discharged with acute coronary syndrome conditions[183]. When compared medication adherence across the United States, a study by Couto found adherence rate were highest in New England and the West North Central region, and followed by the East North Central and the Middle Atlantic region[184]. While the whole south area, including the West south central, the East South Central, and the South Atlantic region had relatively poor adherence. Moreover, similar geographical variation was observed in both Medicare beneficiaries and commercial insurance beneficiaries, and the variation was stable across different therapeutic drug classes (antidiabetics, antihypertensives and antilipidemics). However, these studies did not investigate local-characteristics that might cause the geographical difference in medication adherence.

According to the Andersen's behavioral model of health services use, patients' utilization of health care are influenced by not only patients' own characteristics but also contextual factors, such as structures of the health system and neighborhood socioeconomics[185,186]. Identifying contextual risk factors of medication adherence is helpful to design population-based strategies and have greater impact on health promotion. Therefore, the aim of this study was to explore local variation in medication adherence of ACEIs/ARBs, and examine contextual and individual influences on medication adherence. We hypothesized that medication taking behaviors, in this study, adherence to prescribed ACEIs/ARBs, were associated with both patients' individual characteristics and the characteristics of the neighborhood they lived in. Moreover, we expected that the adherence rate of ACEIs/ARBs were varied across regions in the United State. We also expected the relationship between contextual factors and medication adherence varied across the United States. In this study, we performed Geographically Weighed Regression (GWR) model to test our working hypothesis.

6.3 Methods

6.3.1 Study design and data source

We conducted a retrospective cohort study of Medicare Part D beneficiaries with hypertension and CKD in the United States between 2006 and 2013. This study deign comprised three main periods: a selection period to identify eligible hypertensive CKD patients (from 01/01/2006 to 12/31/2012); a 2-year baseline period to assess patient's history of comorbid conditions and procedures (from 01/01/2006 to 12/31/2007), and a follow-up

period to assess patients' medication compliance from the beginning of 2008 to the end of our study, 12/31/2013.

This study used Medicare 5% sample files from the USRDS databases, which contained individual claims obtained from the CMS Medicare 5% Sample SAFs, ESRD related information extracted from the ESRD Medical Evidence form (CMS 2728), and death related information extracted from the ESRD Death Notification form (CMS 2746) as well as the Master Beneficiary Summary File. To assess the relationship between contextual factors and medication taking behaviors, Medicare claims were further merged with external data resources by state code and county code to obtain contextual information. Information from the U.S. Census Bureau American community Survey (ACS) 5-Year Estimates data (2009-2013) and the Health Resources and Services Administration (HRSA) Primary Care Service Area (PCSA) data (2007) were extracted for contextual characteristics and primary care resources at county level. This unique linked dataset also included spatial information of population center, extracted from the Map of Centers of Population from the U.S. Census Bureau (2008)[148]. Information contained in the final dataset for statistical analyses in this study was completely de-identified.

6.3.2 Study population

We selected all elderly Medicare beneficiaries who had hypertension in the 2-year baseline period and been diagnosed with CKD in the selection period. To capture a complete history of medication use, we then restricted our study subjects to Medicare fee-for-service beneficiaries with continuous prescription drug coverage. Moreover, to assess the one-year medication compliance of ACEIs/ARBs, we further excluded hypertensive CKD patients

who did not have any ACEIs/ARBs claim in the follow-up period, those whose first ACEIs/ARBs claim was after 12/31/2012, as well as those who died within one year period from their first ACEIs/ARBs claim in the follow-up period.

6.3.3 Measures

Medication related outcome measures

One-year ACEIs/ARBs adherence was measured by PDC, which was defined as the percentage of days covered by ACEIs/ARBs in a fixed one year refill interval, starting from the first date of dispensing ACEIs/ARBs. A threshold of 80% PDC was applied to define good medication adherence.

Individual factors

Demographic information like age, gender and race was extracted from the Medicare 5% files. Age was calculated at the baseline, and race was classified as white, black, Asian, others and unknown. Part D coverage was classified into three categories based on their Part D enrollment status in 2008, which included Part D with deemed Low-income Subsidy (LIS), Part D with non-deemed LIS, as well as Part D without LIS. Patients who are dual eligible to Medicare and Medicaid can automatically enroll in LIS (deemed LIS), while the rest eligible LIS beneficiaries whose income level below 150% of the Federal Poverty Level need apply to receive subsidy (non-deemed LIS). All LIS enrollees do not have a prescription gap, also known as “donut hole”, while deemed LIS qualified a 100% subsidy for monthly premium and a lower fixed amount of copy compared to those with non-deemed LIS. Comorbid conditions were assessed in the 2-year baseline period using Medicare claims and following the previously validated algorithm: having at least one inpatient claims or at least two

outpatient claims. We generated separate indicators for conditions associated with kidney dysfunctions, include diabetes, cardiovascular conditions and cardiovascular procedures. We further calculated an adapted Deyo Charlson comorbidity index (CCI) with exclusion of diabetes, renal and cardiovascular conditions[168]. A higher value of CCI indicated a heavier burden of illness.

Contextual factors

Characteristics of contextual factors were assessed at county level. The counties' socioeconomic status was measured by the Townsend deprivation index, a composite score derived from four census statistics: percentage of household without car ownership and home ownership, percentage of household overcrowding (more than 1 person per room), and unemployment rate among people aged 16 and over[155]. A higher Townsend index indicates a higher average level of deprivation. In addition, available primary care resources for each county were measured by the rate of general physicians per 10,000 persons and the percentage of population residing in MUAs. Percentage of residents covered by Medicare was also assessed as a measurement of predisposing characteristics in the county.

6.3.4 Statistical analyses

To conduct descriptive analyses of baseline individual characteristics, study subjects were categorized into two groups based on their medication adherence: a PDC of at least 80% vs. a PDC below 80%. Patients with PDC above 80% were generally considered as being adherent

to prescribed ACEIs/ARBs. We presented the means and standard deviation for continuously variable, and percentages for categorical variables. Group differences in these factors were examined using two-tailed t-tests for continuous variable and chi-square tests for categorical variables. Descriptive statistics of contextual characteristics at county level were reported as well, where patients' one-year PDC and one-year persistence were aggregated to county level.

GWR was utilized to investigate the relationship between contextual factors and medication adherence at county level. We first examined the spatial distribution of medication across counties in the United States. We then developed a multivariate linear regression model, also called global model, to establish a properly specified model for GWR. The redundancy of our explanatory variables was assessed using VIF value, with a cut off at 2. Next, we ran the GWR model and checked the increase in goodness-of-fit through R^2, AICc and Bayesian Information Criterion (BIC). We also compared the statistical performance between the global model and the GWR model through the GWR ANOVA test. Lastly, we conducted the geographical variability test for each explanation variables, which indicated whether the local estimates of the specified variable demonstrated significant spatial variability. The results of GWR model were displayed as maps of local parameter estimates. It was noteworthy that the statistics reported in the GWR model was local t value. We used the da Silva and Fotheringham correction to calculate the adjusted p value at different significant level[187], and further identified the significant parameter estimates in local area[188].

The mixed effect model was performed to assess the association between individual factors, contextual factors, and medication adherence, controlling the random effects of counties. The

statistical significant level was set of $p<0.05$. We used SAS 9.3 for data management, and statistical analysis. The GWR software was used specifically for GWR models.

6.4 Results

Our study cohort consisted of 70,201 aged Medicare beneficiaries with hypertension and CKD who used ACEIs/ARBs during our study period. These patients resided in a total of 2,981 counties in the United States, with an average of 24 persons per county. Approximately 61% of them had one-year PDC of at least 80% (mean=0.9, SD=0.1) while the rest of them had poor adherence (mean=0.5, SD=0.2).

Table 6-1 and 6-2 reported the descriptive statistics of individual characteristics between groups. There was no difference in the distribution of age and having diabetes between patients with good adherence or poor adherence to ACEIs/ARBs. Nevertheless, fewer male and more whites were observed in the good adherence group (male: 38.9% vs. 41.3%; white: 87.9% vs.85.1%). In addition, slightly fewer beneficiaries in the good adherence group were deemed LIS beneficiaries (33.3% vs.34.2%), compared to the poor adherence group. In term of comorbid conditions, patients with poor adherence demonstrated a higher CCI scores compared to those being adherence to ACEIs/ARBs (1.4 vs. 1.2). When assessed patients' history of cardiovascular related conditions and procedures, patients classified into the poor adherence group showed a significantly higher percentage in almost all of investigated conditions and procedures except CABG (shown in table 6-2).

Table 6-3 summarized the descriptive statistics of environmental characteristics in county level. The average PDC of ACEIs/ARBs in a one-year fixed interval was 0.76. The average number of general physician per 10,000 patients was 7. On average, about 14% of total population living in the studied counties had Medicare coverage and approximately 56% of people residing in MUAs. The mean value of the deprivation score among our investigated counties was -0.01, where a higher positive score indicate greater deprivation.

Adherence rate of ACEIs/ARBs in county level were geographically clustered, and the map of medication adherence displayed a geographic variation across the United States (figure 6-1). Results of GWR model were summarized in table 6-4. Overall, negative associations between deprivation score, more people residing in MUAs and medication adherence were observed across the United State, while positive association between number of available physicians per population, percentage of older residents and medication adherence were observed. We also drew maps of the estimated relationship between medication adherence and predictors, which reflect these geographic differences (figure 6-2 - 6-5). Figure 6-2 revealed the West mountain region, the West South Central region and the Northeast region had a significantly strong to moderate negative association between deprivation score and rate of medication adherence. Figure 6-3 displayed the varied association between adherence rate and proportion of population residing in MUAs across the United States. A significantly strong negative association was observed in the Northeast region, the Midwest region and the West region. Figure 6-4 and 6-5 indicated both percentage of older residents and number of available physicians per population were positively associated with medication adherence, and these associations were only significant in the Great Lake region and the New England region, By comparing the goodness of fit statistics, we concluded the GWR model fits our data better than the OLS model.

Results from the mixed effect model indicated that predictors of increased medication adherence include: female, receiving LIS either deemed or non-deemed, having diagnosis of diabetes, having AFIB as well as residing in a county with more available general physician and residing in counties with the oldest population. Meanwhile, heavy comorbidity burden, having cardiovascular conditions, living in the deprived area and region lack of medical resources were associated with poor adherence to ACEIs/ARBs.

6.5 Discussion

This study is, to our knowledge, the first national representative study to examine the spatial variation in adherence to ACEIs/ARBs among CKD patients, and investigate the spatial association between contextual factors and medication adherence across the United States. Approximately 61% of our study subjects were adherent to their prescribed ACEIs/ARBs, defined as having a PDC at least 80%, which is lower than the adherence rate demonstrated in previous studies using claims data or pill counts (from 65% to 70%). The difference may be due to the older age and the great comorbidity burdens in our population.

The average proportion of days covered by ACEIs/ARBs was 76% after aggregating individuals' adherence to county level. Consistent with previous studies, we found there was spatial clustering in adherence to ACEIs/ARBs in our hypertensive CKD cohort[182,183]. Moreover, we observed comparable geographic variation observed in Cuto's study[184]. In our study, the Northeast region and the Midwest region demonstrated better adherence compared to the South region.

Our findings of GWR models indicated adherence to ACEIs/ARBs were related with the characteristics of the place that patients lived in. Previous studies had revealed that accessibility to healthcare were related with neighborhood socioeconomic status, distance and travel time to facilities, and availability of healthcare resources[189–192]. Consistent with previous findings, we found a negative association between medication adherence and living in regions with high deprivation level and lack of primary care resources across the United States. Additionally, by displaying the estimated local relationship in maps, we found the magnitude and significance of the relationship were varied across regions. For example, deprivation score was significantly related with declined medication adherence in the Northeast region, the West South Central region and the Wet mountain region. Proportion of population residing in MUSs reflects the availability of primary care resources. Different with deprivation score, lack of primary care resources were significantly associated with decreased adherence in all regions except the South region, despite the fact that the South region had a more severe shortage of healthcare resource. Results of our study indicate that in the West region, the Midwest region, and the Northeast region, interventions for enhancing medication adherence may consider to target on CKD patients living in the place lack of primary care resources. While in the West Mountain region, the West South Central region and the Northeast region, interventions for medication adherence are recommend to target on patients residing in deprivation counties. Moreover, it is worth to note that neither deprivation score nor lack of primary care resources explained the poor medication adherence in the East South Central and the South Atlantic. Other contextual factors that are not captured in this study may drive the geographical difference in medication adherence, like treatment strategies and healthcare quality[80–82]. A study of high risk medication use found Part D

enrollees who lived in the Southern United Sates were at higher risk of receiving regimens with high risk medication, compared to those lived in the New England area[85].

Besides the contextual factors, our study found patients' adherence to their prescribed medication were also associated with their demographic characteristics, medical conditions, and health plan coverage. In this study, we did not establish a significant relationship between age and medication adherence. This may be attributable to the relatively older age of our population and less variation (SD=7.1 mean=78.6). A review paper by DiMatteo evaluated a total of 568 adherence studies from 1949 to 1988 and found inconsistent relationship between age, gender and treatment adherence[130]. Results of our study also found patients with heavy comorbidity burden had a declined adherence to their prescribed medication, and this may because they have the greater pill burden and more complex regimens[121,134]. Moreover, as what previous studies found, onset of diabetes was associated better adherence to ACEIs/ARBs. This may because ACIEs/ARBs are first-line therapy for patients with diabetic CKD[42]. Additionally, presence of AFIB was associated with better adherence to ACEIs/ARBs, which may attributable to the protective effect of these RAS inhibiting agents on the recurrence of AFIB[193]. With regard to status of Part D coverage, receiving the low income subsidy from Part D was associated with a better adherence. Beneficiaries with LIS may have a lower risk of cost-related medication nonadherence because they are not only receiving subsidy for premium and copayment but also not limited by the coverage gap. A study of patients with kidney failure found patients reduced their medication use when they fell into the coverage gap[194].

There are several limitations in this study. First, as a retrospective cohort study it cannot draw causal inference but only provide associative information. Second, internal validity may be threated due to the characteristics of administrative claim data, selection bias and omitted variable bias. Although our study subjects are all Part D enrollees, we may still not able to fully capture all pharmacy claims, especially among those who have multiple prescription drug coverages. This may result in underestimation of medication adherence. Additionally, patients with hypertension may have a higher risk of experiencing cardiovascular events, such as hospitalization because of coronary disease, heart failure, stroke or peripheral arterial disease. Therefore, further studies are recommend to exclude days of hospitalization in the denominator when calculating medication adherence. Moreover, administrative claims data do not sufficiently reveal actual medication adherence. It is possible that the refills dispensed by pharmacies are not taken by patients, and lead to overestimating of medication consumption. The findings from this study should be interpreted with caution, especially when generalize these results to practice. Although we extracted a large cohort of ACEIs/ARBs users with hypertension and CKD from a nationally representative dataset, sicker patients who died within one year period after filling ACEIs/ARBs were excluded in our study. Meanwhile, patients were required to continuously enroll in Part D. These inclusion and exclusion criteria may cause selection bias. Additionally, because of the security concern, counties with less than ten CKD patients were not included in our spatial analysis, which cause rural areas may be under represented in this study. Third, this study was lack of self-report measures, like patients' perceived need of medications, perceived benefits of medications, side effects and effective physician-patient communications. These subjective factors are related with patients' medication taking behaviors. Future research is warranted to conduct qualitative studies to understand local barriers to appropriate medication use and medication adherence. Meanwhile, researchers can perform spatial

analyses with both individual characteristics and contextual characteristics in small local regions. Then, researchers and healthcare providers could design population based strategies in the local area to promote medication compliance in CKD patients, from perspective of population.

6.6 Conclusion

Medication adherence to ACEIs/ARBs is varied across the United States, where Northeast region and Midwest region illustrate better medication adherence than South region. Different risk factors and modifiable factors at both individual level and contextual level have been detected in this study. Additionally, our study displays the geographic variation of the relationship between environmental characteristics and medication adherence, which help us understand the place effects behind these relationships. This information is valuable in policy implication in local area, especially when researchers and practitioners implement local interventions to improve medication use among hypertensive CKD patients in the United States.

Table 6-1 Descriptive Statistics of individual demographic characteristics among elderly patients with hypertension and chronic kidney disease (CKD) by status of ACEIs/ARRs adherence (n=70,201)

Variable#	*PDC above 80% (n=42,733) **	*PDC below 80%(n=27,468)*	*All (n=70,201)*
Baseline characteristics	*Mean (SD)/%*	*Mean/%*	*Mean/%*
Age (years)	78.6 (7.1)	78.6 (7.1)	78.6 (7.1)
Age (years)			
<70	12.7	12.7	12.7
70-75	22.7	22.7	22.7
75-80	23.2	23.3	23.3
>80	41.4	41.4	41.4
Male	38.9	41.3	39.9
Race			
White	87.9	85.1	86.8
Black	8.8	11.3	9.8
Asians	1.7	1.6	1.7
Others	1.5	1.8	1.6
Unknown	0.1	0.1	0.1
Prescription coverage at baseline			
Part D without LIS	64.3	63.8	64.1
Part D with non-deemed LIS	2.4	2.1	2.3
Part D with deemed LIS	33.3	34.2	33.7
Diabetes mellitus (DM)	45.3	45.8	45.5
Charlson comorbidity index $	1.2 (1.7)	1.4 (1.8)	1.3 (1.7)

* Continuously enrolled in Medicare A&B from 2006/1/1 and continuously enrolled in Medicare Part D from 2007 to end of 2013/date of death were required. A two-year baseline period was applied (2006-2007) to evaluate baseline characteristics, and a one-year baseline period (2007) was used to examine medication use history. Patients without any claim of ACEIs/ARBs were excluded.

Significant difference was observed in all variables except age ($P<0.05$)

$ Adapted Charlson comorbidity index was calculated by excluding diabetes, kidney diseases and cardiovascular diseases

Table 6-2 Descriptive Statistics of cardiovascular-related characteristics among elderly patients with hypertension and chronic kidney disease (CKD) by status of ACEIs/ARRs adherence (n=70,201)

Variable #	*PDC above 80% (n=42,733)**	*PDC below 80% (n=27,468)*	*All (n=70,201)*
Cardiovascular Comorbidities$			
ASHD	48.52	53.71	50.55
AMI	11.44	13.68	12.32
CHF	30.88	35.91	32.85
CVA-TIA	29.67	33.26	31.08
PAD	36.82	40.51	38.26
AFIB	20.63	21.79	21.08
SCA/VA	5.47	6.45	5.85
Other Cardiovascular diseases	44.95	49.2	46.61
Cardiovascular Procedures			
PCI	3.61	4.46	3.94
CABG	1.32	1.4	1.35
ICD/CRT-D	0.78	1.01	0.87

* Continuously enrolled in Medicare A&B from 2006/1/1 and continuously enrolled in Medicare Part D from 2007 to end of 2013/date of death were required. A two-year baseline period was applied (2006-2007) to evaluate baseline characteristics, and a one-year baseline period (2007) was used to examine medication use history. Patients without any claim of ACEIs/ARBs were excluded,
# Significant difference was observed in all variables except CABG ($P<0.05$)
$ Abbreviations: ASHD, atherosclerotic heart disease; AMI, acute myocardial infarction; CHF, congestive heart failure; CVA/TIA, cerebrovascular accident/transient ischemic attack; PAD, peripheral arterial disease; AFIB, atrial fibrillation; SCA/VA, sudden cardiac arrest and ventricular arrhythmias; PCI, percutaneous coronary interventions; CABG, coronary artery bypass grafting; ICD/CRT-D, implantable cardioverter defibrillators/cardiac resynchronization therapy with defibrillator devices.

Table 6-3 Descriptive Statistics of environmental characteristics in county level (n=2981)

*Variable**	*Mean*	*SD*
ACEIs/ARBs adherence (PDC)	0.76	0.12
Numbers of patients per county	23.50	57.36
Number of General physicians per 10,000 persons	6.96	4.33
Percent of Medicare Beneficiaries in Total Population	0.14	0.04
Proportion of People Residing in Medically Underserved Areas	0.56	0.45
Deprivation score#	-0.01	2.79

*A total of 70,201 elderly patients with hypertension and chronic kidney disease resided in 2,981 counties.
Deprivation score was measured by Townsend index, which incorporating unemployment rate, percentage of households without care ownership, home ownership and overcrowding.

Table 6-4 The association between environmental characteristics and average ACEIs/ARBs adherence at county level using Geographically Weighted Regression (n=1522)

County level Variable*	Mean of Estimate	Standard Error	Min	Lower Quartile	Median	Upper Quartile	Max
Number of General physicians per 10,000 persons	0.0008	0.0006	0.0000	0.0003	0.0006	0.0013	0.0026
Percent of Medicare Beneficiaries in Total Population	0.1738	0.0911	0.0126	0.0932	0.1608	0.2415	0.3609
Proportion of People Residing in Medically Underserved Areas	-0.0178	0.0075	-0.0278	-0.0252	-0.0189	-0.0116	-0.0007
Deprivation score#	-0.0028	0.0008	-0.0057	-0.0032	-0.0028	-0.0023	-0.0013

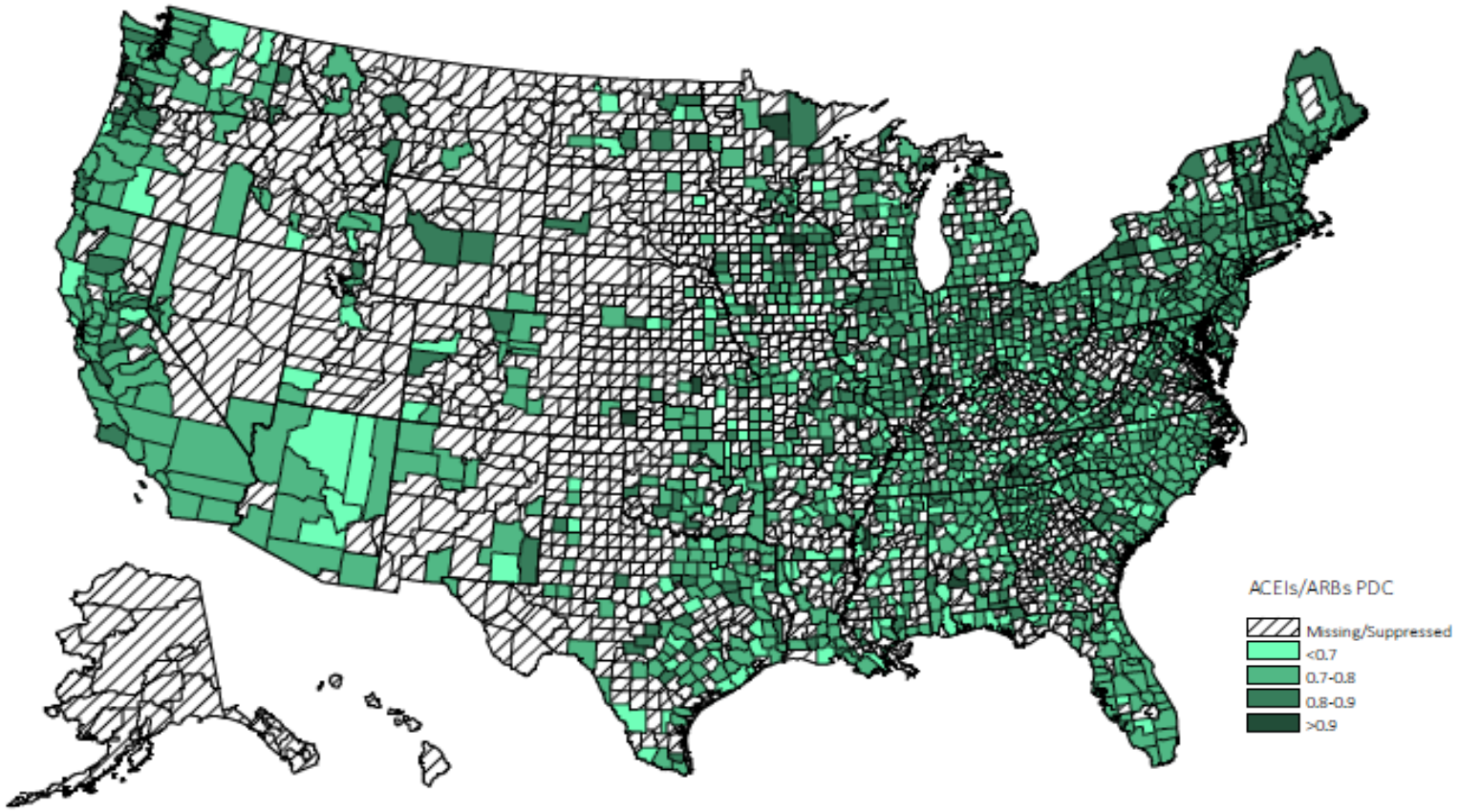
*Counties with less than ten CKD patients were excluded.
Deprivation score was measured by Townsend index, which incorporated unemployment rate, percentage of households without care ownership, home ownership and overcrowding.

Table 6-5 The association between individual, environmental characteristics and ACEIs/ARBs adherence at individual level using Mixed model (n=70,201)

Variable	Estimate	Standard Error	Pr > |t|	
Age (years)	0.000	0.000	0.924	
Charlson comorbidity index	-0.005	0.001	<.0001	***
Female	0.010	0.002	<.0001	***
Race (White)				
Black	-0.034	0.004	<.0001	***
Asians	0.001	0.008	0.8788	
Others	-0.019	0.008	0.0186	*
Unknown	-0.044	0.031	0.1462	
Prescription coverage at baseline (Part D without LIS)				
Part D with non-deemed LIS	0.018	0.007	0.0066	**
Part D with deemed LIS	0.012	0.002	<.0001	***
Diabetes mellitus (DM)	0.011	0.002	<.0001	***
ASHD	-0.010	0.002	<.0001	***
AMI	-0.008	0.003	0.0135	*
CHF	-0.016	0.003	<.0001	***
CVA-TIA	-0.009	0.002	<.0001	***
PAD	-0.007	0.002	0.0013	**
AFIB	0.006	0.003	0.0352	*
SCA/VA	-0.002	0.005	0.7011	
Other Cardiovascular diseases	-0.010	0.002	<.0001	***
PCI	-0.010	0.005	0.065	
CABG	0.010	0.009	0.2743	
ICD/CRT-D	-0.002	0.011	0.8431	
Number of General physicians per 10,000 persons	0.001	0.000	0.0035	**
Percent of Medicare Beneficiaries in Total Population	0.081	0.033	0.0123	*
Proportion of People Residing in Medically Underserved Areas	-0.013	0.003	<.0001	***
Deprivation score#	-0.001	0.000	0.0002	***

Deprivation score was measured by Townsend index, which incorporating unemployment rate, percentage of households without care ownership, home ownership and overcrowding.

Figure 6-1 Distribution of 1 year ACEIs/ARBs adherence



*Counties with less than ten CKD patients were excluded

Figure 6-2 Townsend deprivation score (distribution, β & p-value)

*Counties with less than ten CKD patients were excluded

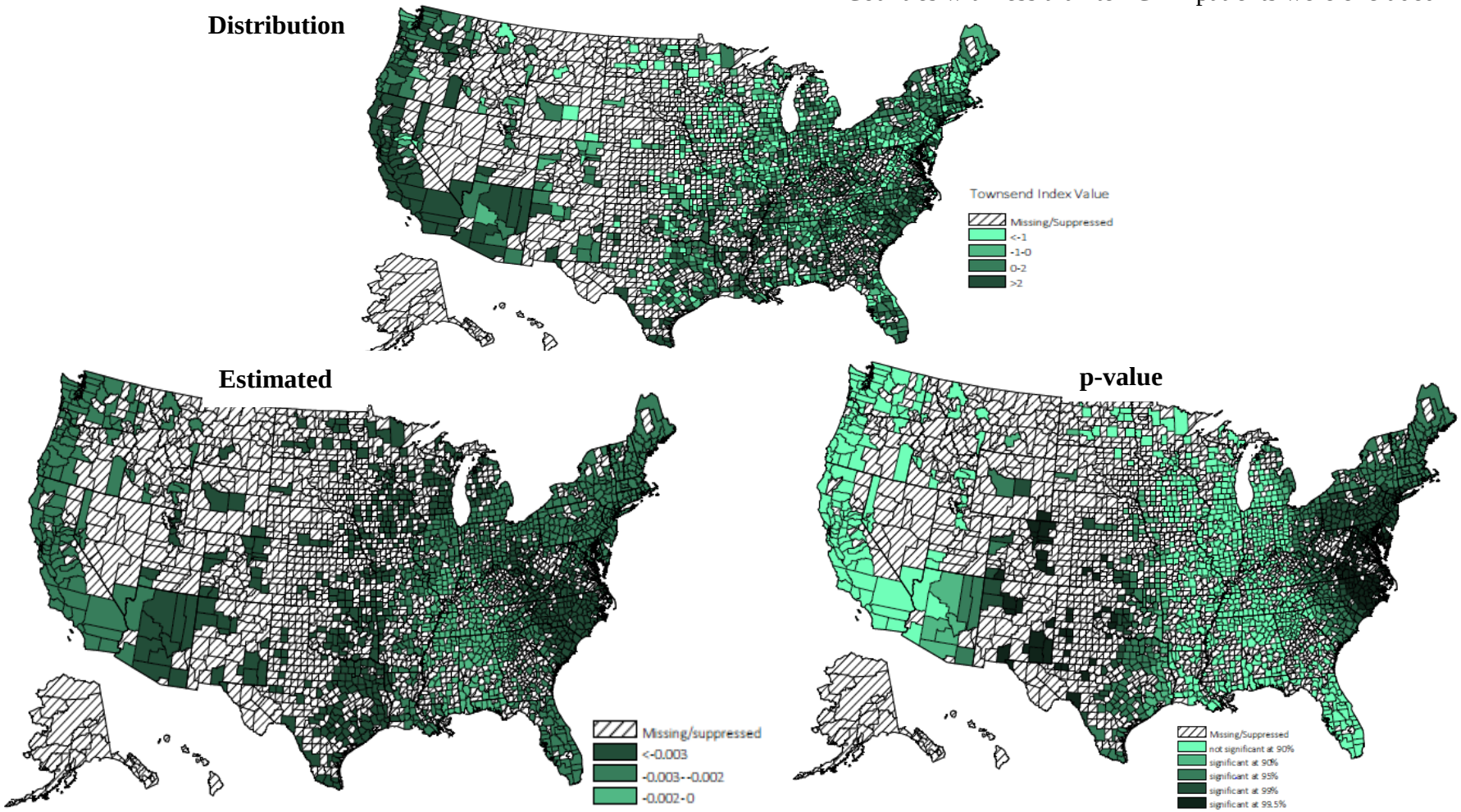
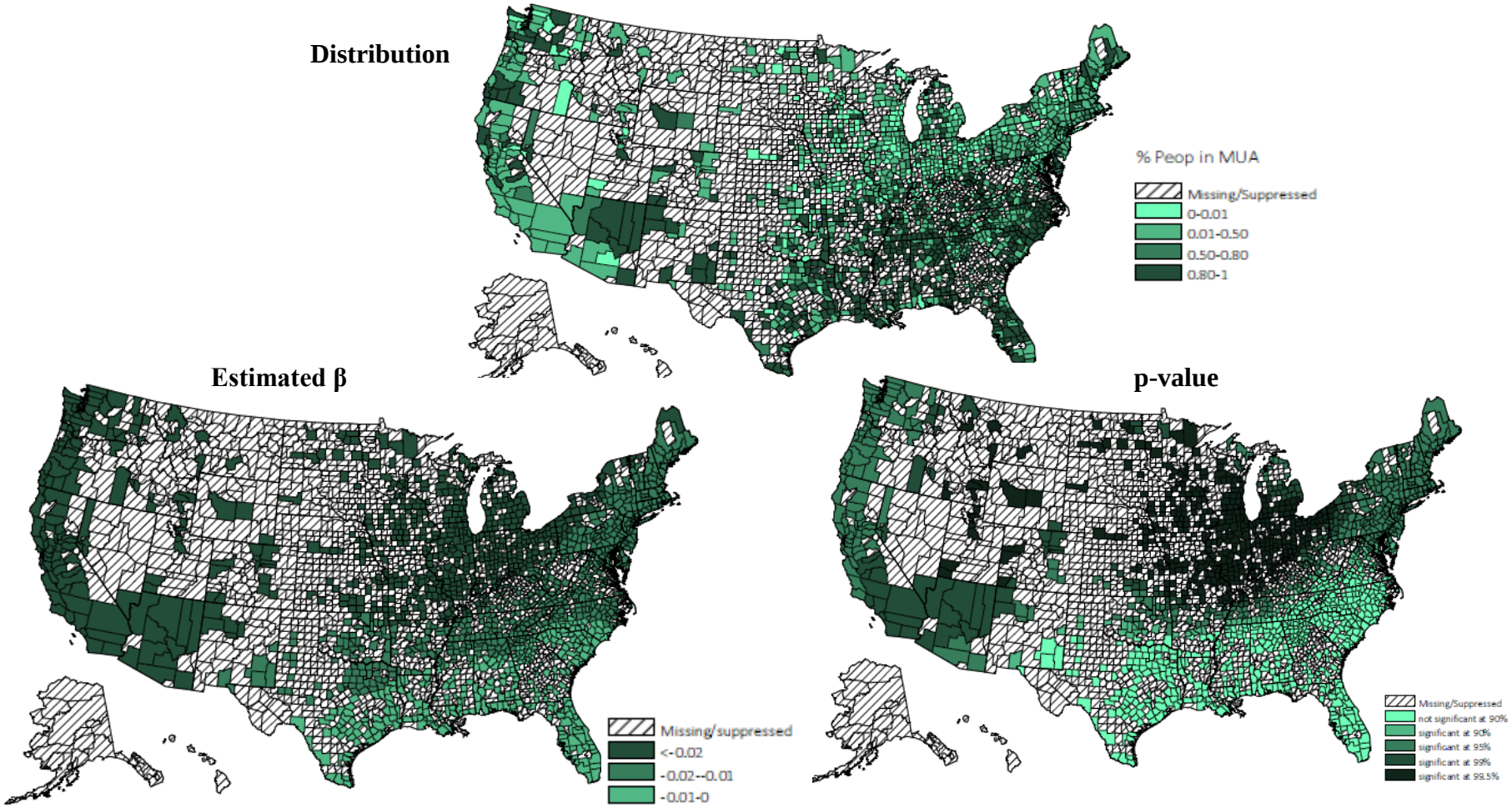
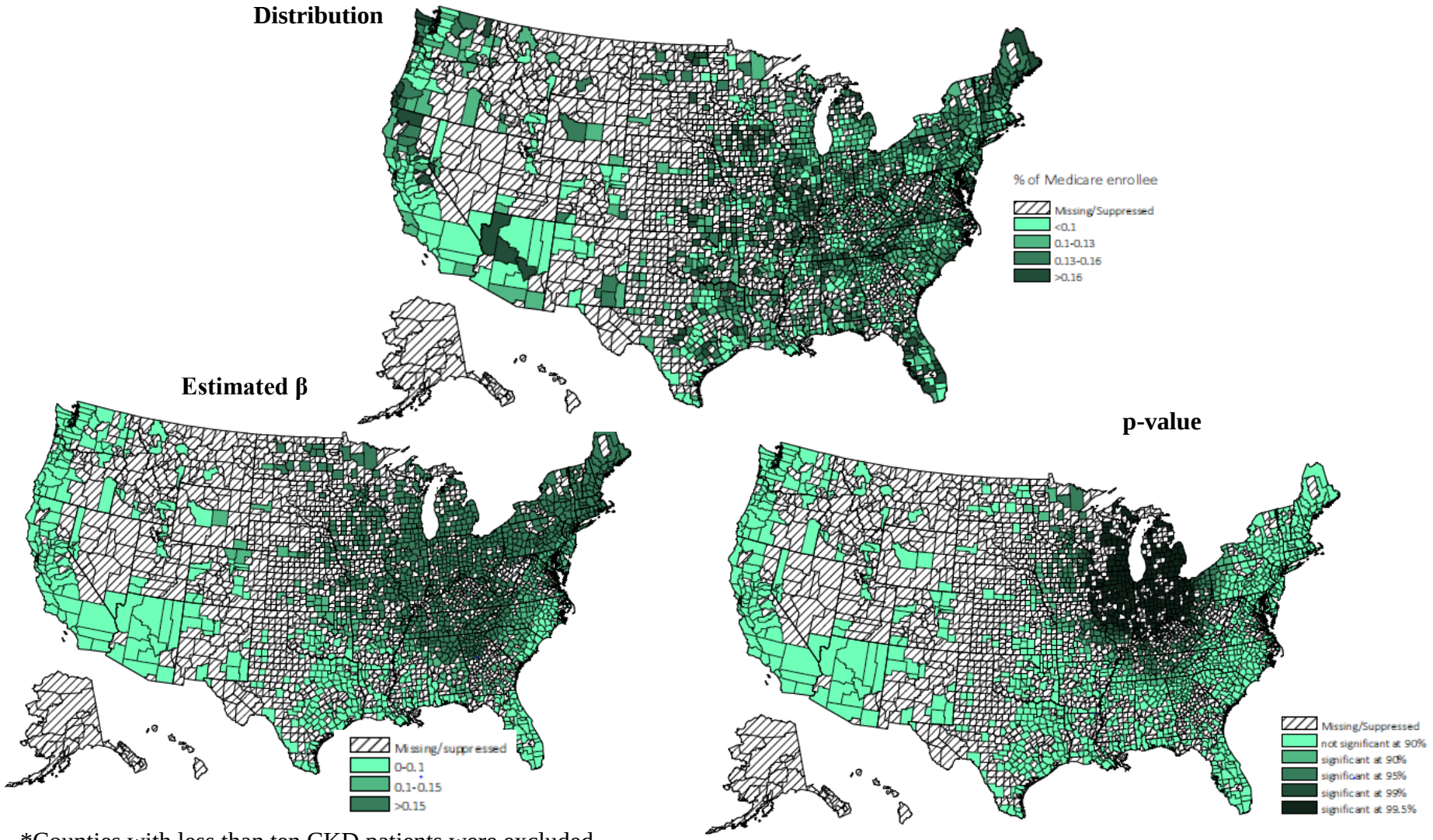


Figure 6-3 Proportion of population residing in MUAs (distribution, β & p-value)



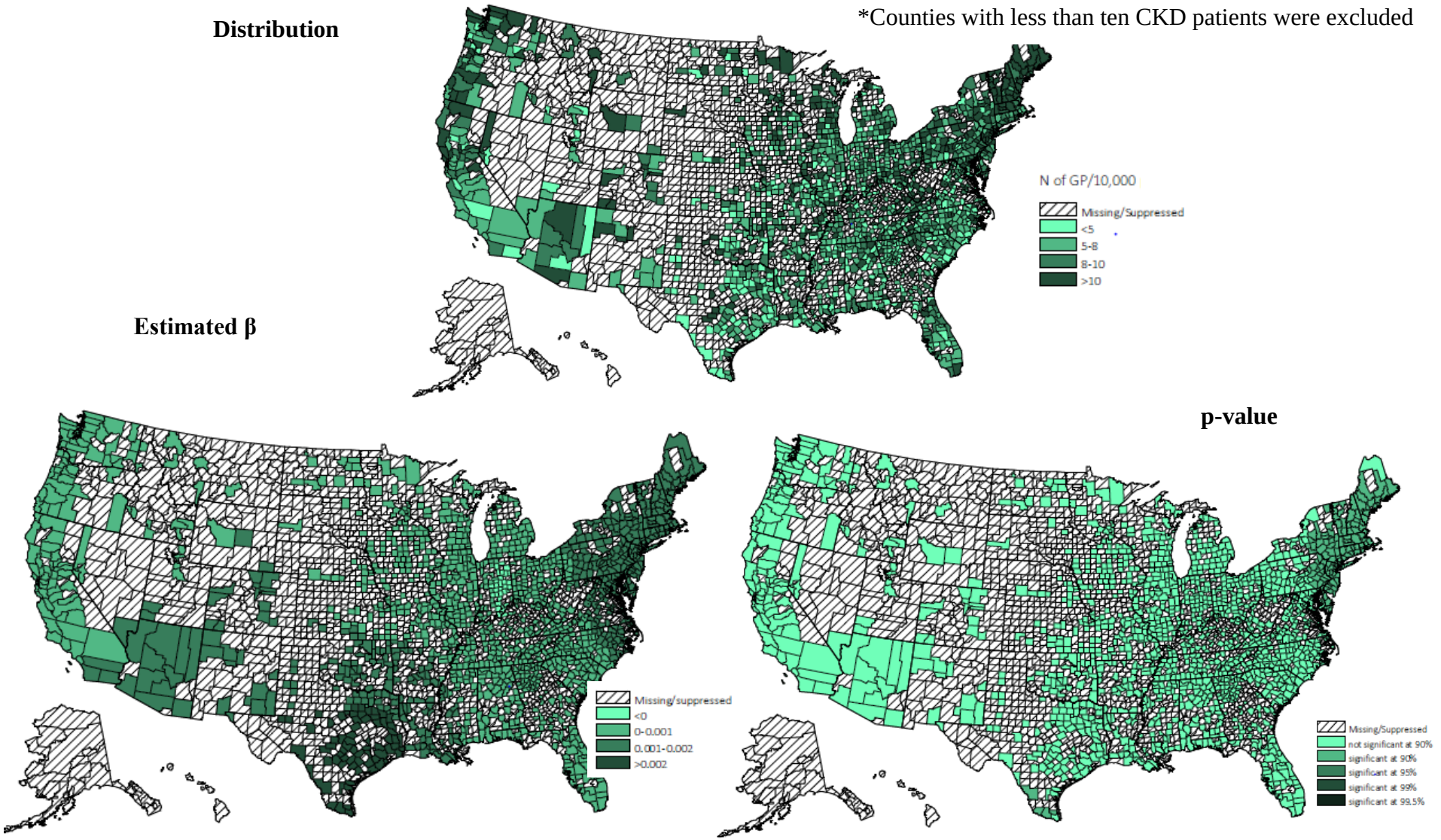
*Counties with less than ten CKD patients were excluded

Figure 6-4 Proportion of Medicare beneficiaries (distribution, β & p-value)



*Counties with less than ten CKD patients were excluded.

Figure 6-5 Number of general physicians/10,000 population (distribution, β, and p value)



Chapter 7

OVERALL CONCLUSION

Over 15% of Americans have CKD, and approximately 74% of them have coexisting hypertension. Although uncontrolled blood pressure is a previously established risk factor of CKD progression, only 28% of CKD patients have made their blood pressure under-controlled[1]. The objectives of this dissertation were to assess the relationship between access to cardiovascular medications, medication use behaviors, and CKD outcomes among elderly patients with hypertension and CKD in the United States. This study is innovative in sense of providing a geographic approach to explore factors that associate with medication adherence. In addition, this study is significant in term of systematically assessing the long-term benefits of being adherent to prescribed cardiovascular agents in improving outcomes for hypertensive CKD patients. To achieve our study goals, we used a large combined dataset which contained Medicare claims, census data, primary care resources data and spatial information.

This dissertation work is comprised of three study aims, and findings from each of the three study aims contribute to the overall objective of the study. First, the study presented in chapter four evaluated cardiovascular agents use patterns in elderly patients with hypertensive CKD, and further investigated the association between different pharmacologic

therapies and CKD outcomes. Then, the second study in chapter five examined the long-term benefits of adherence to prescribed cardiovascular agents in CKD outcomes among elderly patients with CKD and hypertension. Finally, the last study in chapter six examined geographic variation in medication adherence across the United State at first, and then explored individual and contextual factors that were associated with medication compliance among old adults with CKD and hypertension.

7.1 Major findings

In chapter four, we first evaluated incident CKD patients' medication use pattern using a six-month period after the date of first diagnosis of CKD. A total of six most commonly used cardiovascular agents were investigated: ACEIs, ARBs, calcium channel blockers, beta-blockers, diuretics and statins. Consistent with previous studies, a heavy pill burden was observed in our study cohort as well, as more than half of hypertensive CKD patients were on combination therapies[88]. However, there was still about 22% of patients were not receiving any of investigated medications, and only half of patients received guideline-recommended ACEIs/ARBs. Our findings reveal that there is a need to promote cardiovascular agents use, particularly use of ACEIs/ARBs, in hypertensive CKD patients. Second, we assessed the association between different pharmacologic therapies and CKD outcomes, and we found patients receiving therapies including ACEIs/ARBs and statins demonstrated better treatment outcomes. Lastly, we explored factors that were associated with using ACEIs/ARBs and found patients who enrolled Part D low-income subsidy program were less likely to receive recommended ACEIs/ARBs. These patients are typically facing the lowest premiums and copayment, and having no coverage gap. Our findings may indicate the existence of barriers to accessing guideline-recommended prescriptions beyond cost in this vulnerable population.

In chapter five, we established an approach to systematically evaluate long-term benefits of adherence to cardiovascular agents for elderly patients with hypertension and CKD. We performed the Cox proportional hazards regression analyses with medication adherence as time-varying covariates to assess the association between adherence to cardiovascular agents and CKD progression, as well as all-cause mortality. Our findings showed consistently good adherence to ACEIs/ARBs, as well as other cardiovascular agents, was associated with substantial decreased risk of developing ESRD and mortality. It was worthy to note that medication adherence rate of investigated drug classes was suboptimal at baseline, ranged from 50% to 60%. Overall, our findings indicate there is a need for improving medication compliance, particularly regarding the long-term medication adherence.

In chapter six, we found there was geographical variation in adherence to ACEIs/ARBs among hypertensive CKD patients who used ACEIs/ARBs, as patients residing in the West North Central and New England region demonstrated a relatively better adherence than those residing in the East South Central and West South Central regions. Then, we implied an innovative approach to explore how contextual factors were associated with adherence at county level using geographically weighted regression model. By using this spatial analysis, we were able to incorporate the spatial autocorrelation when model medication adherence as a function of potential predictors, and provide visualized results. Our study results found residing in MUAs and place with high deprivation score were associated with poor adherence, while living in counties with more old adults and having more available physicians were associated with increased adherence. Besides contextual factors, individual factors like prescription drug coverage and comorbidities were also related with poor adherence. Receiving Part D LIS was associated with increased medication adherence, as Part

D LIS beneficiaries have no coverage gap and in turn may less like to experience cost-related medication nonadherence.

7.2 Study implications and future research

This dissertation research raises several implications for the care of CKD patients. First, this study emphasized the importance of utilization and use behaviors of cardiovascular agents in CKD treatments. Our study found both utilization rate and medication compliance of cardiovascular agents, especially guideline-recommended ACEIs/ARBs, were suboptimal in elderly patients with CKD and hypertension. Interventions are needed to improve utilization rate of both ACEIs/ARBs and other cardiovascular agents, particularly regarding the long-term adherence. There is evidence to suggest that interventions with clinical pharmacy activities have benefits for CKD patients[195–197]. These interventions performed by pharmacists generally include medication review, identification of drug-related problems, providing therapeutic recommendations, laboratory monitoring, as well as patient counselling and education, while few of them have components that target on promoting medication compliance[198,199]. Moreover, there is lack of high-quality research to evaluate the effectiveness of clinical pharmacy services on CKD outcomes. Further studies are warranted to develop interventions to promote medication compliance, and add indicators of medication compliance as criteria for evaluating medication management interventions for CKD patients. Second, findings from this study may help healthcare providers make informed treatment decisions. For example, according to our findings, adding ACEIs/ARBs and statins to anti-hypertensive therapy is recommended for patients with hypertension and CKD. Finally, our study revealed the geographic variation of the relationship between contextual factors and medication adherence. This information is critical for policy makers to allocate health care resources, and in turn improve medication taking behaviors and therapeutic treatment

outcomes. Moreover, individual and contextual predictors of medication adherence found in our study are helpful for researchers and healthcare providers to identify CKD patients at high risk of medication nonadherence.

On the basis of current literature, including this study, several directions may be warranted for future research. First, apply the spatial analysis in a local region to identify communities where medication compliance is suboptimal. Meanwhile, conduct qualitative studies to understand local barriers to appropriate medication use and medication adherence, and then design population based strategies in local area to promote medication compliance in CKD patients, from perspective of population. Lastly, additional studies are needed to explore the geographical variation in processes of care in CKD patients across the United States.

7.3 Study limitations

This dissertation work has some limitations. First, the retrospective cohort study design cannot draw causal inferences. Second, Medicare 5% claims files are lack of data for beneficiaries who enroll in Medicare Advantage plan. Thus, our study cohort was limited to Part D enrollees who were not covered by Medicare Advantage plan. In addition, the restricted selection criteria may result in selection bias. For example, to capture all pharmacy claims, we excluded patients who were not continuously enrolled in Part D over the study period, which results in a study cohort with slightly older age, having a higher percentage of female, non-white, diabetes and cardiovascular conditions. Third, this study may suffer from omitted variable bias. For instance, hospitalization was not adjusted when we examined the association between medication adherence and CKD outcomes, which may bias our results to unknown directions (Chapter 5). Our next step is to add a time-varying covariate of

hospitalization to the survival model. Moreover, there is no laboratory data in Medicare 5% claims files. For this reason, we were lack of direct measurement of blood pressure and kidney function. We also not able to assess subjective factors, like patients' awareness of , patients' perceived need of medication, perceived efficacy of medication, concerns of side effects, as well as physician-patient communications. These qualitative variables are previously established determinates of medication adherence in qualitative studies[132,133]. Fourth, pharmacy claims do not sufficiently reveal actual medication taking behaviors. Patients may not take their prescribed medications following recommendations. Moreover, we are not able to fully capture all pharmacy claims, if patients obtain medications from outside resources other than Medicare Part D. Finally, a certain number of counties were excluded in spatial analysis because of the security concern (Chapter 6). This may bias our results as rural areas may be under represented in the study.

7.4 Overall conclusion

The use of cardiovascular agents is the corner stone for the treatment of hypertensive CKD. Although there are significant benefits from medication use on delaying the progression of CKD and reducing mortality risk, the utilization rate of these medications and their long-term adherence, especially guideline-recommended ACEIs and ARBs, are suboptimal among elderly adults with hypertension and CKD. In addition, geographical variation exists in medication adherence in the United Sates, and patients' medication adherence is associated with both individual and contextual characteristics. Developing local interventions to promote medication compliance for patients with CKD and hypertension are thus warranted.

APPENDICES

University of Michigan IRB

Han, Yun

From: eresearch@umich.edu
Sent: Thursday, December 15, 2016 4:37 PM
To: rb9ap@virginia.edu; hanyun@umich.edu; rhirth@umich.edu; rsaran@umich.edu; serick@umich.edu
Subject: eResearch Notification: Notice of Exemption for (HUM00107765)

Health Sciences and Behavioral Sciences Institutional Review Board (IRB-HSBS) • 2800 Plymouth Rd., Building 520, Room 1170, Ann Arbor, MI 48109-2800 • phone (734) 936-0933 • fax (734) 998-9171 • irbhsbs@umich.edu

To: Yun Han

From:

There are no items to display

Cc:

Rajesh Balkrishnan
Yun Han
Richard Hirth
Rajiv Saran
Steven Erickson

Subject: Notice of Exemption for [HUM00107765]

SUBMISSION INFORMATION:
Title: Medication Adherence Outcomes in Elderly Patients with Hypertension and Chronic Kidney Disease: a Geographical Approach
Full Study Title (if applicable): Medication Adherence Outcomes in Elderly Patients with Hypertension and Chronic Kidney Disease: a Geographical Approach
Study eResearch ID: HUM00107765
Date of this Notification from IRB: 12/15/2016
Date of IRB Exempt Determination: 12/15/2016
UM Federalwide Assurance: FWA00004969 (For the current FWA expiration date, please visit the UM HRPP Webpage)
OHRP IRB Registration Number(s):

IRB EXEMPTION STATUS:
The IRB HSBS has reviewed the study referenced above and determined that, as currently described, it is exempt from ongoing IRB review, per the following federal exemption category:

EXEMPTION #4 of the 45 CFR 46.101.(b):
Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the

1

investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

Note that the study is considered exempt as long as any changes to the use of human subjects (including their data) remain within the scope of the exemption category above. Any proposed changes that may exceed the scope of this category, or the approval conditions of any other non-IRB reviewing committees, must be submitted as an amendment through eResearch.

Although an exemption determination eliminates the need for ongoing IRB review and approval, you still have an obligation to understand and abide by generally accepted principles of responsible and ethical conduct of research. Examples of these principles can be found in the Belmont Report as well as in guidance from professional societies and scientific organizations.

SUBMITTING AMENDMENTS VIA eRESEARCH:
You can access the online forms for amendments in the eResearch workspace for this exempt study, referenced above.

ACCESSING EXEMPT STUDIES IN eRESEARCH:
Click the "Exempt and Not Regulated" tab in your eResearch home workspace to access this exempt study.

Thad Polk
Chair, IRB HSBS

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