INVESTIGATING THE LONGITUDINAL PATTERNS OF USE AND COMPARATIVE EFFECTIVENESS OF BETA BLOCKER THERAPY IN THE HEMODIALYSIS POPULATION

Magdalene Marie Assimon

A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology in the Gillings School of Global Public Health.

Chapel Hill
2017

Approved by:

M. Alan Brookhart

Jason P. Fine

Jennifer E. Flythe

Gerardo Heiss

J. Bradley Layton

ABSTRACT

Magdalene Marie Assimon: Investigating the longitudinal patterns of use and comparative effectiveness of beta blocker therapy in the hemodialysis population
(Under the direction of M. Alan Brookhart)

United States hemodialysis patients experience high rates of cardiovascular mortality. Approximately 50% of deaths are due to cardiovascular disease. In the general population, beta blocker treatment improves clinical outcomes in a range of cardiovascular conditions. However, the cardioprotective benefit of beta blocker therapy has never been evaluated by large randomized trials in individuals receiving maintenance hemodialysis therapy, a population with special drug dosing considerations. Pharmacologic and pharmacokinetic differences across individual beta blockers may alter drug efficacy and safety profiles in the setting of end-stage renal disease. Using the clinical research database of a large United States dialysis provider linked with the United States Renal Data system registry we assembled a cohort of maintenance hemodialysis with Medicare insurance coverage who initiated beta blocker therapy from 2007 – 2012 to: 1) assess long-term beta blocker utilization patterns in the hemodialysis population, 2) examine the association between beta blocker adherence versus non-adherence (proportion of days covered (PDC) $\geq$ 80% versus PDC < 80%) and all-cause mortality, and 3) evaluate the association between carvedilol versus metoprolol initiation and 1-year all-cause and cardiovascular mortality.

First, we found that carvedilol and metoprolol were the most commonly initiated beta blockers (79.7% of all beta blocker new-users). After beta blocker initiation, therapy cessation (i.e. discontinuation) and re-initiation were relatively common. Second, we found that beta blocker adherence (versus non-adherence) was associated with lower all-cause mortality (PDC $\geq$ 80%

versus < 80% measured using pharmacy claims: adjusted hazard ratio (HR) [95% confidence interval (CI)] = 0.84 [0.79, 0.90]). Finally, we found that carvedilol (versus metoprolol) initiation was associated with higher all-cause (adjusted HR [95% CI] = 1.09 [1.02, 1.16]) and cardiovascular mortality (adjusted HR [95% CI] = 1.19 [1.08, 1.30]). The potential mechanism for the observed mortality association may be the increased rate of intradialytic hypotension observed after carvedilol (versus metoprolol) initiation.

Our findings provide insights into: 1) the longitudinal patterns of beta blocker utilization among individuals receiving maintenance hemodialysis therapy, 2) the association between beta blocker adherence and all-cause mortality, and most importantly, 3) provide important evidence to guide beta blocker prescribing in hemodialysis population the absence of clinical trial data.

ACKNOWLEDGEMENTS

I have received tremendous support, guidance, and encouragement over the years. My adviser, Alan Brookhart, has been in an incredible resource throughout my doctoral training. In every meeting or interaction I have with Alan, I always learn something new. He has helped me develop my methodologic toolbox and critical thinking skills. I am very thankful for his support, kindness, and patience. I would also like to especially thank Jenny Flythe who has been an incredible mentor and adviser throughout this dissertation and over the course many other research projects. Jenny supported my intellectual curiosities, while always providing me with critical evaluation and much needed direction. I am truly grateful for the time, energy, and effort that Jenny has provided to help me learn and grow as an independent clinician-researcher. She has taught me a great deal about science, leadership, and collaboration. My time at UNC would not have been the same without Jenny's mentorship. I would also like to thank Gerardo Heiss whose positive attitude and practical advice helped guide me forward during my doctoral training. In addition, Bradley Layton and Jason Fine have provided excellent epidemiologic and statistical support throughout this dissertation. I am very grateful for the extremely astute feedback that my dissertation committee (Alan, Jenny, Gerardo, Bradley and Jason) has provided on my research.

Over the past few years, I have had the amazing opportunity to train at the UNC Kidney Center. I was honored to be selected as a post-doctoral trainee on the UNC Kidney Center's NIH/NIDDK funded Renal Epidemiology Training Grant (T32 DK007750). I would like to thank Jenny Flythe, Ronald Falk, Gerald Hladik, Susan Hogan, Abhi Kshirsagar, and all of the faculty

and staff at the UNC Kidney Center. They have provided a welcoming and intellectually stimulating training environment, which promoted my growth as a clinician-researcher.

In addition, under the direction of Alan Brookhart and Jenny Flythe, I successfully obtained external funding to support my dissertation work. I was awarded an Ruth L. Kirschstein Post-Doctoral National Research Service Award from the NIH/NIDDK (F32 DK109561).

Finally, I would like to extend a special thanks to my friends and family for their unwavering support, and for always providing a reason to set aside work for a minute to enjoy life.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACE	Angiotensin converting enzyme
BLOCADE	Beta Blocker to Lower Cardiovascular Dialysis Events
BP	Blood pressure
CI	Confidence interval
CMS	Centers for Medicare & Medicaid Services
COPD	Chronic obstructive pulmonary disease
CV	Cardiovascular
D/C	Discontinuation
DOPPS	Dialysis Outcome Practice Patterns Study
ESRD	End-stage renal disease
FDA	Food and Drug Administration
GI	Gastrointestinal
HEMO	Hemodialysis
HR	Hazard ratio
ICD-9	International Classification of Diseases, Ninth Revision
IPT	Inverse probability of treatment
IRR	Incidence rate ratio
MI	Myocardial infarction
No.	Number
OR	Odds ratio
PAAD	Pharmaceutical Assistance to the Aged and Disabled
PACE	Pharmaceutical Contract for the Elderly in Pennsylvania

PDC	Proportion of days covered
PVD	Peripheral vascular disease
p-y	Person-years
Ref.	Referent
Rx	Prescription
SNF	Skilled nursing facility
U.S.	United States
USRDS	United States Renal Data System

CHAPTER 1: SPECIFIC AIMS

United States (U.S.) hemodialysis patients experience exceedingly high rates of cardiovascular mortality, nearly 50% of deaths are attributed to cardiovascular causes. In the general population, pharmaceutical interventions such as beta blockers improve clinical outcomes among individuals with hypertension, heart failure, atrial fibrillation and post-myocardial infarction. The cardioprotective benefit of beta blocker therapy has never been evaluated in large randomized trials among hemodialysis patients, a population with unique pharmacokinetic and hemodynamic considerations. Pharmacologic and pharmacokinetic differences across individual beta blockers may alter drug efficacy and safety profiles in the setting of end-stage renal disease (ESRD). Despite this evidence void, over 60% of hemodialysis patients receive beta blockers. A clear understanding of the longitudinal patterns of beta blocker use in a real-world setting combined with a rigorous assessment of the comparative effectiveness of the most commonly used beta blockers in the U.S. is urgently needed to improve clinical decision making and to guide beta blocker prescribing in the hemodialysis population. Using the clinical research database of a large U.S. large dialysis provider linked with the U.S. Renal Data System (USRDS), the following specific aims were addressed in this dissertation.

Aim 1: An investigation of the long-term beta blocker utilization patterns in the hemodialysis population to:

1A. Characterize and describe beta blocker initiators by beta blocker subtype (e.g. non-selective, cardioselective, and alpha beta blockers) and individual generic products.

1B. Estimate the cumulative incidence of beta blocker discontinuation and switching after initiation:

- Overall (among all beta blocker initiators).
- Among carvedilol and metoprolol initiators (separately).

1C. Estimate the cumulative incidence of beta blocker re-initiation after beta blocker discontinuation:

- Overall (among all beta blocker discontinuers).
- Among carvedilol and metoprolol discontinuers (separately).

Aim 2: To examine the association between beta blocker adherence (proportion of days covered ≥ 80%) versus non-adherence (proportion of days covered < 80%) and all-cause mortality when:

2A. The proportion of days covered is computed using standard methods (i.e. using administrative pharmacy claims only).

2B. The proportion of days covered is computed using modified methods (i.e. using administrative pharmacy claims and also accounting for time periods when patients were admitted to the hospital or a skilled nursing facility using inpatient/outpatient claims).

Aim 3: To evaluate the association between carvedilol versus metoprolol initiation and 1-year all-cause and cardiovascular mortality, overall and within clinically relevant subgroups (including patients with: hypertension, atrial fibrillation, heart failure, and a recent myocardial infarction).

CHAPTER 2: BACKGROUND AND SIGNIFICANCE

The public health importance of reducing cardiovascular risk among hemodialysis patients and the potential role of beta blocker therapy

Hemodialysis patients possess a tremendous cardiovascular disease burden, which contributes to unacceptably poor outcomes. Compared to individuals without kidney disease, cardiovascular mortality rates are 5 to 7-fold higher among individuals receiving maintenance hemodialysis.[1] Cardioprotective medications such as beta blockers, among others, are often prescribed as a means to reduce cardiovascular risk across several conditions (e.g. hypertension, atrial fibrillation, heart failure and post-myocardial infarction). However, clinical trials establishing the cardioprotective nature and safety of beta blocker therapy largely excluded hemodialysis patients,[2, 3] a population with special drug dosing considerations.

Currently, due to a lack of population-specific evidence,[4] clinicians are forced to apply beta blocker clinical trial data that was generated in non-dialysis patient cohorts to those receiving maintenance hemodialysis. Pharmacologic and pharmacokinetic differences across individual beta blockers may alter medication safety and efficacy profiles in the setting of ESRD. Pharmacologically, beta blockers differ with respect to their beta-adrenergic receptor selectivity and vasodilatory capabilities. Kinetically, physiochemical factors, such as molecular size, hydrophilicity, plasma protein binding, and the volume of distribution influence the extent of beta blocker clearance by the hemodialysis procedure (i.e. dialyzablity). These key differences may plausibly alter the hemodynamic and antiarrhythmic risk-benefit profiles of individual beta blockers in the setting of ESRD. Thus, given the widespread use of beta blocker therapy in the

hemodialysis population, understanding the comparative safety and effectiveness of individual beta blocker medications is essential for determining optimal cardiovascular treatment strategies in this vulnerable patient group.

Brief overview of beta blocker pharmacology

Beta blockers (also termed beta-adrenergic blocking agents, beta-antagonists, beta-adrenergic antagonists, beta-adrenoreceptor antagonists or beta-adrenergic receptor antagonists) are a class of drugs that are commonly used in the management of cardiovascular disorders. There are 3 main subclasses of beta blocker medications including non-selective beta blockers (propranolol, pindolol, nadolol, sotalol, timolol), cardioselective beta blockers (acebutolol, atenolol, betexolol, bisoprolol, metoprolol, nebivolol) and alpha-beta blockers (carvedilol, labetalol). Cardioselective and alpha-beta blockers are the beta blocker subtypes most commonly prescribed to hemodialysis patients. Metoprolol (tartrate and succinate), a cardioselective beta blocker, and carvedilol, an alpha-beta blocker carvedilol, account for nearly 80% beta blocker prescriptions the U.S. dialysis population.[5] Thus, the remainder of this chapter will often highlight metoprolol and carvedilol.

Beta blocker medications are competitive antagonists. Competitive antagonists are drug molecules that bind to specific target receptors located in the body and have no subsequent biologic effect (i.e. they do not activate the target receptors). Antagonistic medications compete with available agonist molecules (endogenous proteins or hormones that bind to and activate target receptors resulting in a subsequent biologic effect) for binding sites on target receptors. When a sufficient concentration of an antagonist is systemically available, it will displace the agonist from receptor binding sites, resulting in a lower frequency of target receptor activation and effectively reducing the magnitude of the corresponding physiologic effect.

Not surprisingly, the various beta blocker medications possess different pharmacologic properties. Once in systemic circulation, these medications compete with catecholamines (e.g. epinephrine and norepinephrine) for binding at target receptors located in several tissues throughout the body. Metoprolol is a cardioselective beta blocker. Metoprolol acts mainly on the heart, with a high specificity for the beta-1 adrenergic receptor. In contrast, carvedilol is an alpha-beta blocker. Carvedilol acts on the heart, vasculature and other tissues, blocking beta-1, beta-2 and alpha-1 adrenergic receptors. Both medications reduce heart rate and cardiac contractility by blocking beta-1 receptors in the sinoatrial node and myocardium. In contrast, carvedilol has additional vasodilatory effects due to its antagonistic action on alpha-1 receptors located in blood vessels. Furthermore, carvedilol has some activity at beta-2 receptors located in the lungs, liver and pancreas, which may lead to the occurrence of side effects such as bronchoconstriction (due to the antagonistic effect of carvedilol on the lungs) increases in serum glucose (due to the antagonistic effects of carvedilol on the liver and pancreas) and hyperkalemia (due to its antagonistic effects on beta-2-receptors, carvedilol may impair the epinephrine-mediated the movement of extracellular potassium into the cells).

Brief overview of beta blocker pharmacokinetics

Pharmacokinetics is the quantitative description of drug disposition in the human body, including drug absorption, distribution, metabolism and elimination. Hemodialysis may affect drug pharmacokinetics, and in some cases drug dosing adjustments are required. The need for a dosage adjustment arises when a significant fraction of the drug or its active metabolites are cleared from systemic circulation by the hemodialysis procedure (termed drug dialyzablity). In such cases, a change in the dosing regimen, such as the administration of supplemental doses following the dialysis procedure, may be needed to maintain the drug's therapeutic effect. Physiochemical

factors, such as molecular weight, hydrophilicity, plasma protein-binding, and the volume of drug distribution, in the body are key medication properties which determine a medications's level of dialyzablity.

Individual medications within the beta blocker class display considerable pharmacokinetic heterogeneity, differing with regards to half-life, hydrophilicity, plasma protein-binding, volume of distribution, sites of metabolism, and route of elimination. A striking pharmacokinetic difference between these medications is their route of elimination. The main route of elimination of metoprolol (tartrate and succinate) and its corresponding metabolites is renal excretion (5 to10% as unchanged drug), whereas carvedilol and its metabolites are primarily excreted in the feces.[6-8] In addition, due to their physiochemical characteristics (**Table 2.1**),[6-8] metoprolol is highly dialyzable and carvedilol is minimally dialyzable (comparing metoprolol to carvedilol, hemodialytic clearance: 148 versus 18 mL/min; fraction of elimination due to hemodialysis: 13% versus 4%).[9]

Brief overview of the beneficial cardiovascular effects of beta blocker therapy in hypertension, heart failure, atrial fibrillation, and post-myocardial infarction

Despite the fact that approximately half of all deaths in the hemodialysis population are due to cardiovascular disease, evidence guiding the treatment of cardiovascular conditions in ESRD is non-existent. Treatment protocols and regimens must be extrapolated from the general population evidence-base. According to current cardiovascular guidelines, beta blocker therapy is indicated and should be initiated after a myocardial infarction,[10, 11] and among patients with heart failure or left ventricular dysfunction.[12] In addition, beta blockers are also given to control heart rate in patients with atrial fibrillation, to control angina, and for symptom management in a number

of other non-cardiovascular disorders such as migraines and anxiety. Even though beta blockers have anti-hypertensive effects, in the absence of the prior aforementioned cardiovascular indications, they are not recommend as first-line therapy in the treatment of essential hypertension, particularly in patients over 60 years of age.[13-15] Atrial fibrillation, heart failure, and coronary artery disease are common in the U.S. hemodialysis population, with a prevalence of approximately 35%, 40%, and 10% respectively.[16-18] Thus, the beneficial effects of beta blocker therapy in the setting of atrial fibrillation, heart failure and myocardial infraction (a sequelae of coronary artery disease) are reviewed below.

Atrial fibrillation

Atrial fibrillation is an abnormal heart rhythm characterized by the loss of the regular and organized contraction of the left atrium and a subsequent increase in ventricular rate. In the typical patient with untreated atrial fibrillation, the ventricular rate can reach 150 beats/minute or higher (normal resting heart rate = 60 to 100 beats/minute), often leading to the occurrence symptoms that impair both functional status and quality of life such as heart palpitations, weakness, fatigue, lightheadedness, dizziness, confusion, and shortness of breath. In addition to providing patients with anticoagulation as a means to prevent thromboembolism, a major goal of atrial fibrillation management is to mitigate symptoms using either a rate-control strategy (e.g. treatment with a chronotropic medication to reduce heart rate) or a rhythm control strategy (e.g. treatment with an anti-arrhythmic drug to maintain sinus rhythm after cardioversion).[19] Oral beta blockers are widely used as primary therapy for rate control in chronic atrial fibrillation. These medications block the activity of catecholamines (e.g. epinephrine, norepinephrine) at beta-1 receptors in the sinoatrial node of the heart, subsequently slowing cardiac conduction through the atrioventricular node. This reduction in conduction decreases ventricular rate and ultimately leads to an improvement in associated symptoms.

Heart failure

Heart failure is a progressive clinical syndrome resulting from changes in cardiac structure and/or function that inhibits the ability of ventricles to fill with or eject blood. Heart failure can be due to abnormalities in systolic function, diastolic function, or both. The majority of heart failure present in individuals receiving maintenance hemodialysis is due to systolic dysfunction (also known as heart failure with reduced ejection fraction). Population-based estimates vary, but indicate that 35 to 70% of hemodialysis patients have left ventricular hypertrophy.[20, 21] In the general heart failure population with systolic dysfunction, clinical trials have shown that treatment with beta blockers slows heart failure progression and improves survival.[22] This general population evidence is supported by a small randomized trial conducted in hemodialysis patients with dilated cardiomyopathy, which demonstrated that treatment with the alpha-beta blocker carvedilol (versus placebo) reduced mortality.[23]

In heart failure, chronic stimulation of cardiac beta receptors, caused by increased sympathetic activity, leads to progressive worsening of ventricular function, as well as systemic and pulmonary vasoconstriction. Beta blocker administration upregulates myocardial beta-1 receptor density in patients with heart failure, helping to restore the inotropic and chronotropic responsiveness of the myocardium. This subsequently results in heart rate reduction and an improvement in cardiac contractile function.[24, 25] In addition, beta blockers reduce the circulating level of vasoconstrictors, renin and endothelin. The corresponding vasodilatory effect leads to a decrease in cardiac afterload, thereby reducing the rate of ventricular hypertrophy and the development of cardiac dysfunction.[25]

Post-myocardial infarction

An acute myocardial infarction, or heart attack, is clinical or pathologic myocardial necrosis caused by ischemia. Most often, a disruption in the vascular endothelium associated with

an unstable atherosclerotic plaque stimulates the formation of an intracoronary thrombus that occludes coronary artery blood flow. This obstruction leads to the death of myocardial tissue downstream of the blockage. Based upon clinical trials conducted in the general population, it is well established that treatment with a beta blocker among acute myocardial infarction patients reduces infarct size and the risk of early death, and also lowers the risk of mortality when therapy is continued long term.[26]

The beneficial effects of beta blocker therapy among myocardial infraction patients result from the antagonism of beta-1 receptors on the heart. These physiologic benefits include: decreased cardiac oxygen demand due to beta blocker induced reductions in heart rate, blood pressure, and cardiac contractility; reduction in cardiac remodeling and improvement in left ventricular hemodynamic function; improved left ventricular diastolic function with a less restrictive filling pattern; an increased ventricular fibrillation threshold, lowering the risk of sudden cardiac death; and inhibition of platelet aggregation and thromboxane synthesis.[27]

Beta blocker utilization in the hemodialysis population

Roughly 60% of U.S. hemodialysis patients use beta blocker medications.[28] A clear and detailed understanding of the patterns of beta blocker utilization is critical prior to designing comparative effectiveness/safety studies, since the occurrence of clinical outcomes and adverse events are often contingent on longitudinal drug exposure (i.e. time on therapy, and current therapy utilization). Thus, a well-designed, comprehensive patterns of use study, describing longitudinal beta blocker utilization (beta blocker discontinuation, switching and re-initiation post-discontinuation), is needed. Currently, the existing evidence-base is weak.[5, 28-41] The majority of epidemiologic studies evaluating beta blocker utilization among individuals receiving maintenance hemodialysis have been cross-sectional in nature. In addition, most of these

investigations evaluated the beta blocker class as a whole, and provide limited, if any, information on utilization patterns of beta blocker subclasses or individual agents. The major findings of the most contemporary, large-scale observational studies of beta blocker utilization among hemodialysis patients are summarized below.

Using data from the USRDS, Frankenfield *et al.* described the use of cardiovascular drugs in 225,635 hemodialysis and peritoneal dialysis patients with continuous Medicare Part D coverage during 2007.[28] Beta blockers were the most commonly used cardiovascular medication class with 64% of study patients filling at least 1 beta blocker prescription during the study period. Among patients with hypertension, atrial fibrillation and a history of a prior myocardial infarction myocardial infraction, beta blocker utilization was highly prevalent. A total of 74%, 69% and 79% of study patients with the respective cardiovascular comorbidities used a beta blocker. Similarly, an investigation using dialysis unit medical record data revealed that beta blocker therapy was commonly used by hemodialysis patients. Specifically, St. Peter *et al.* aimed to describe the patterns of blood pressure medication use among 12,159 incident hemodialysis patients treated at a large U.S. dialysis organization (Dialysis Clinic Incorporated) between 2003 and 2008.[5] In this cohort, 60% of patients were using a beta blocker at 6 months after starting dialysis, with 41% of patients using either a cardioselective or non-selective beta blocker and 19% of patients using an alpha-beta blocker. Metoprolol (53% of patients) and carvedilol (25% of patients) were the most commonly used agents.

While the data documenting the prevalence of beta blocker utilization has been well described in both small dialysis clinic-based studies and large-scale cross-sectional hemodialysis patient cohorts,[5, 28-40] data characterizing the longitudinal use of these medications across time is limited to a single investigation. In a cohort of 33,381 incident hypertensive dialysis patients dually

eligible for Medicaid and Medicare insurance from the years 2000 to 2005, Wetmore *et al.* used the proportion of days covered (PDC) metric to describe long-term use of anti-hypertensive medications including beta blockers.[42] The maximum study follow-up time was 5 years. Additionally, both prevalent and new beta blocker users were included in this cohort. The PDC was computed as follows: (the number of days a patient had a medication of interest available during follow-up) / (the patient's total number of follow-up days) x 100%. A total of 24,818 study patients used beta blocker therapy and were considered in descriptive PDC analyses. The authors found that on average, individuals had beta blocker therapy available for a mean ± standard deviation of 53% ± 31% of days during study follow-up. Differences in proportion of days covered by beta blocker subclass or across individual beta blocker medications (e.g. metoprolol or carvedilol) were not evaluated. While this investigation was the first to describe beta blocker use across time among dialysis patients, it only provides a crude measure of long-term beta blocker utilization patterns. The PDC is a simple metric that describes the percentage days during follow-up each patient had drug available. We are not able to discern more precise patterns of medication utilization, for instance if a patient discontinued beta blocker therapy completely or if the patient was intermittently using beta blockers across time. Recently, there has been increased interest in evaluating the association between longitudinal cardiovascular medication adherence (measured using PDC) and all-cause mortality among individuals with kidney disease.[43] However, PDC calculation methods, which rely on outpatient prescription pharmacy claims, likely require special computational considerations in the in the hemodialysis population. In particular, time periods spent in the hospital or a skilled nursing facility, where medications are provided to patients by the institutional pharmacies and prescription drug benefit-derived home medication supplies are not utilized by patients, are typically ignored in standard PDC calculations and warrants exploration.

Beta blocker therapy and clinical outcomes in the hemodialysis population

Randomized controlled trials

Existing randomized controlled trial data assessing the association between beta blocker therapy and hard clinical outcomes is limited to 3 small studies. First, in a study of 114 Neapolitan hemodialysis patients with dilated cardiomyopathy and an ejection fraction ≤ 35%, participants were randomized to receive either the alpha-beta blocker carvedilol or placebo.[23] After 2 years of treatment, those treated with carvedilol had smaller heart chamber diameters and a higher ejection fraction compared placebo group, suggesting an attenuation of cardiac remodeling with carvedilol. These findings were accompanied by a survival advantage, demonstrating that treatment with carvedilol lowered both all-cause, hazard ratio (HR) [95% confidence interval (CI)] = 0.51 [0.32, 0.82], and cardiovascular mortality, HR [95% CI] = 0.32 [0.18, 0.57]. In addition, time to first hospitalization was lower among patients receiving carvedilol, HR [95% CI] = 0.44 [0.25, 0.77]. Second, in a study of 200 American hemodialysis patients with hypertension and left ventricular hypertrophy, participants were randomized to receive the cardioselecive beta blocker atenolol (dosed three times a week on after hemodialysis treatments) or the angiotensin converting enzyme inhibitor lisinopril (dosed daily)[44] The primary outcome for this study was change in left ventricular mass index at 12 months. However, this trial was terminated early because of a cardiovascular safety issue. The occurrence of the composite cardiovascular safety outcome (myocardial infarction, stroke, hospitalization for heart failure or cardiovascular death) was higher in the lisinopril group as compared to the atenolol group, incidence rate ratio (IRR) [95% CI] = 2.29 [1.07, 5.21]. In addition, the incidence rate of all-cause hospitalizations was higher in the lisinopril group as compared to the atenolol group, IRR [95% CI] = 1.61 [1.18, 2.19]. The results of this trial suggest that treatment with atenolol-based anti-hypertensive therapy may be superior

to lisinopril-based anti-hypertensive therapy for preventing cardiovascular morbidity and all-cause hospitalizations. Finally, the Beta Blocker to Lower Cardiovascular Dialysis Events (BLOCADE) Study was a pilot investigation designed to assess the feasibility of conducting a randomized controlled trial evaluating the effect treating patients with the alpha-beta blocker carvedilol or placebo on all-cause mortality among hemodialysis patients.[45] The target enrollment for this study was 150 hemodialysis patients. A total of 1,443 hemodialysis patients across 11 dialysis units in Australia and New Zealand were screened for study eligibility. Three hundred and fifty-four patients (354) were met study eligibility criteria, and of these individuals 91 patients consented to participate in the study and 74 patients were enrolled (i.e. started the initial run-in phase). During a 6-week run-in phase, all study patients were treated with carvedilol. After completing the run-in phase, participants were randomized to treatment with either carvedilol or placebo and followed for 12 months. Of the 72 patients that entered the run-in phase, only 49 patients went on to enter the randomization phase. A total of 5 patients (7%) withdrew from the trial during the run-in phase due to the occurrence of severe bradycardia or hypotension, established adverse side effects of carvedilol therapy. In randomization phase, participants treated with carvedilol had a higher, but statistically insignificant, rate of intradialytic hypotension (i.e. low blood pressure during hemodialysis defined as a decrease in systolic blood pressure $\geq$ 20 mmHg accompanied by hypotensive symptoms that required treatment) versus those receiving placebo (7 versus 2 events/100 hemodialysis treatments, $p = 0.1$). The results of this feasibility trial suggest that: 1) recruiting a large number of hemodialysis into a randomized controlled trial of beta blocker therapy (versus placebo) will be challenging; and 2) beta blocker tolerability may impact therapy persistence in the hemodialysis population.

Observational studies evaluating the beta blocker use—mortality association

Observational studies examining the relationship between beta blocker therapy and mortality in the hemodialysis population have mainly focused on comparing beta blocker users to non-users. For the most part, existing epidemiologic evidence (**Table 2.2**) suggests that beta blocker therapy, as a class, may reduce all-cause and cardiovascular mortality. However, the results of these studies should be interpreted with their limitations in mind. First, employment of a prevalent user design will miss outcome events that occur early in follow-up (i.e. events occurring right after beta blocker initiation). Second, use of a non-beta blocker comparator group could generate biased effect estimates due to the presence of substantial residual confounding by indication. Beta blocker non-users are likely different from patients randomized to placebo. Non-users may not have a medical indication for beta blocker therapy, they may have used beta blockers in the past and stopped due to a side effect, or they may have contraindications to the beta blocker therapy. Finally, a common scenario nephrology providers face when prescribing beta blockers is deciding which beta blocker they should treat their hemodialysis patients with, rather than deciding if they should treat their patient with a beta blocker versus no therapy. Thus, data from comparative studies that evaluated beta blocker use versus non-use may be of limited clinical utility.

Additional research on the comparative effectiveness/safety of beta blockers in the hemodialysis population is needed

Existing observational evidence suggests that the potential survival benefit conferred by beta blockers may differ across agents. To date, only two observational studies have considered head-to-head beta blocker comparisons. Weir *et al*. assessed the association between beta blocker dialyzability and 180-day mortality in a cohort of 6,588 elderly (>66 years of age), hemodialysis patients treated at dialysis units in the province of Ontario, Canada between 2002 and 2011.[46]

Initiation of a highly dialyzable beta blocker (acebutolol, atenolol, metoprolol tartrate) versus a minimally dialyzable beta blocker (bisoprolol and propranolol) was significantly associated with higher all-cause mortality, adjusted odds ratio [95% CI] = 1.4 [1.1, 1.8]. This study provided initial evidence that beta blocker heterogeneity may differentially impact clinical outcomes in the hemodialysis population. However, carvedilol and metoprolol succinate, which account for approximately 50% of all beta blocker prescriptions in the U.S.[5] were not considered in this study due to provincial prescription formulary restrictions limiting their use. Metoprolol (tartrate and succinate) is a cardioselective beta blocker and is extensively cleared by hemodialysis. Carvedilol is a non-selective beta blocker with additional alpha-blocking effects and is minimally cleared by hemodialysis.

In another observational study, Shireman *et al*. evaluated the association between beta blocker selectivity and mortality in a cohort of 4,398 incident U.S. hemodialysis and peritoneal dialysis patients with dual Medicare/Medicaid coverage and hypertension.[47] Initiation of a cardioselective beta blocker (atenolol, metoprolol) versus a non-selective beta blocker (carvedilol, labetalol) was associated with lower 5-year all-cause mortality, adjusted HR [99% CI] = 0.84 [0.72, 0.97]. However, the relative contributions of carvedilol and metoprolol, the most commonly beta blockers prescribed to individuals receiving maintenance dialysis in the U.S., to the observed association are unclear. Furthermore, this investigation relied on data from 2000 to 2005, prior to the introduction of the Medicare Part D prescription drug benefit, and also used a study population comprised of patients new to dialysis therapy with dual Medicare and Medicaid insurance coverage. Currently, prevalent dialysis patients (individuals with a dialysis vintage > 1 year) comprise roughly 60 to 70% the ESRD population, and the vast majority of individuals receiving maintenance dialysis therapy (approximately 80%) are enrolled in Medicare Part D,[48] indicating

that a contemporary analysis evaluating the association between beta blocker initiation and clinical outcomes in a representative patient cohort is needed.

While a head-to-head randomized clinical trial would be the ideal approach to investigating the comparative safety and efficacy of individual beta blockers in the dialysis population, recent data from the BLOCADE feasibility study suggested that recruitment for such a trial may be challenging.[45] Well-designed pharmacoepidemiologic studies are thus needed to inform clinical decision-making. A hallmark feature of a well-designed comparative effectiveness/safety study is that the medications being compared to one another represent clinically meaningful treatment choices. Real-world treatment decisions are based on numerous factors a such as the severity of the underlying disease-state, as well as patients' general health status and patient preferences. Confounding by indication can be minimized by choosing to evaluate medications with the same (or very similar) indications, contraindications, and routes of administration. A notable limitation of the studies by Weir *et al.* and Shireman *et al.* is that the beta blockers studied have different therapeutic roles in the setting of contemporary clinical nephrology practice. The beta blocker medications that were contrasted may not represent exchangeable treatment alternatives, and thus indication bias may have influenced the results. For instance, in the case of the Weir study, the Food and Drug Administration (FDA) labeled indications of the highly dialyzable beta blocker metoprolol include angina, heart failure, hypertension, and post-myocardial infarction,[6, 7] whereas the only FDA labeled indication for the minimally dialyzable bisoprolol is hypertension.[49] Similarly, in the Shireman study, the cardioselective beta blocker metoprolol has a greater number of cardiovascular indications (previously mentioned) as compared to the to the non-selective beta blocker labetalol (hypertension is in the only FDA labeled indication of this medication).[50] Given these clinical limitations, a large-scale, comparative study assessing the association between

initiation of the most commonly used beta blockers with similar indication profiles (metoprolol and carvedilol) and mortality is needed to inform cardiovascular clinical decision making in the U.S. hemodialysis population.

The differential pharmacologic and pharmacokinetic profiles of carvedilol and metoprolol may impact the cardioprotective nature of these medications in the unique end-stage renal disease environment

Clinical evidence from the general population suggests that the relative efficacy of individual beta blockers may differ across cardiovascular disease states.[51-56] Meta-analyses of randomized controlled trials indicate that treatment with the vasodilating beta blocker carvedilol may improve left ventricular function and survival to a greater extent than the cardioselective beta blocker metoprolol in the general, non-dialysis heart failure population.[51, 52] Even though the findings from this meta-analysis suggest treatment with carvedilol (versus metoprolol) may result in better clinical outcomes in heart failure, these benefits may not translate to individuals receiving maintenance dialysis. Specific to the hemodialysis population, the marked pharmacologic and pharmacokinetic heterogeneity between metoprolol carvedilol in combination with the unique ESRD environment (i.e. exposure to frequent hemodynamic and electrolyte shifts), may alter the risk-benefit profiles of these medications. Thus, we cannot rely on general population beta blocker data to guide prescribing practices when treating individuals receiving maintenance hemodialysis.

Although carvedilol and metoprolol are both beta blockers, their pharmacologic sites of action differ. As previously described, metoprolol (tartrate and succinate) is a cardioselective beta blocker (blocks beta-1 adrenergic receptors), whereas carvedilol is a non-selective beta blocker (blocks both the beta-1 and beta-2 adrenergic receptors) with additional alpha-blocking properties

(blocks alpha-1 adrenergic receptors). Due to their action on the cardiac-based beta-1 receptor, both metoprolol and carvedilol reduce heart rate and cardiac contractility. Since carvedilol also has activity at the alpha-1 receptor, it is a peripheral vasodilator. Precipitous drops in blood pressure (i.e. episodes of intradialytic hypotension) during the hemodialysis procedure are common, occurring in approximately 10 to 70% of treatments (depending on the definition).[57] Mechanistic studies indicate that hemodynamic compromise during the hemodialysis treatment results in the hypoperfusion of vital vascular beds, leading to ischemic damage to the heart[58, 59] and other major organs.[60-62] Over time, repeat episodes of hypotension-induced cardiac ischemia will result in cardiac hypertrophy and fibrosis and corresponding downstream adverse cardiac effects, including heart failure, arrhythmia, and ultimately death. In fact, the occurrence of more frequent intradialytic hypotension has been associated with increased all-cause and cardiovascular mortality.[57, 63, 64] The vasodilatory properties of carvedilol may influence intradialytic blood pressure and thus hemodynamic stability. It is possible that carvedilol-induced alpha-1 blockade may blunt compensatory sympathetic nervous system-mediated peripheral vasoconstriction during ultrafiltration, increasing the likelihood that intradialytic hypotension will occur.

Carvedilol also has the potential to impact serum electrolyte concentrations. Antagonism of the beta-2 receptor inhibits movement of extracellular potassium into cells. Administration of carvedilol, a beta blocker with beta-2 activity, may increase serum potassium levels and the associated arrhythmia risk. Pre-dialysis hyperkalemia is common, making hemodialysis patients particularly vulnerable to the potassium-raising effect of beta-2 blockade. Carvedilol-induced hyperkalemia has been reported in patients with kidney disease.[65]

In addition to the potential adverse pharmacologic-related effects, differences in carvedilol and metoprolol pharmacokinetics may influence cardiovascular outcomes. As noted previously,

metoprolol is extensively cleared by hemodialysis and carvedilol is minimally cleared by hemodialysis. Acutely, the rapid removal of metoprolol from systemic circulation during the hemodialysis may put patients at an increased risk for the occurrence ventricular arrhythmias and sudden death. In the long-term, the repeated removal of metoprolol during hemodialysis treatments (i.e. on an every-other day basis) may diminish its beneficial cardioprotective effects longitudinally. On the other hand, since carvedilol is not readily dialyzable it is possible that carvedilol's antihypertensive effects are maintained during hemodialysis treatments, possibly increasing the risk of hemodynamic instability.

Tables

Table 2.1 Physiochemical properties of metoprolol and carvedilol that impact their dialyzablity

Property	Metoprolol tartrate	Metoprolol succinate	Carvedilol
Molecular weight	684.8 Daltons	652.8 Daltons	406.5 Daltons
Hydrophilic	No (moderately lipophilic)	No (moderately lipophilic)	No (highly lipophilic)
Plasma protein binding	~12% bound to plasma proteins (mainly albumin)	~12% bound to plasma proteins (mainly albumin)	> 98% bound to plasma proteins (mainly albumin)
Volume of distribution	3.2 to 5.6 L/kg	3.2 to 5.6 L/kg	1.2 – 1.8 L/kg

Table 2.2 Observational studies assessing beta blocker use versus non-use and mortality

Author (Year)	Study type	Population	Main findings[a]
Foley (2002)[16]	Cohort study	11,142 hemodialysis patients followed in the USRDS Dialysis Morbidity and Mortality Waves 3 and 4 Study receiving dialysis on 12/31/1993	Baseline beta blocker use versus non-use was associated with ↓ all-cause mortality - HR (95% CI) = 0.84 (0.75, 0.93)
Griffith (2003)[66]	Cohort study	2,877 incident hemodialysis and peritoneal dialysis patients enrolled in the USRDS Morbidity and Mortality Study Wave 2 study in 1996 and who were on anti-hypertensive therapy	Baseline beta blocker use versus non-use was not significantly associated with all-cause and CV mortality - All-cause death: HR (95% CI) = 0.94 (0.84, 1.06) - CV death: HR (95% CI) = 1.05 (0.89, 1.25)
Berger (2003)[67]	Cohort study	1,025 ESRD patients treated with hemodialysis or peritoneal dialysis who hospitalized for an acute myocardial infraction and were enrolled in both the USRDS and the Cooperative Cardiovascular Project	Beta blocker administration during hospitalization for acute MI versus no beta blocker treatment was associated with ↓ 30 day all-cause mortality - OR (95% CI) = 0.78 (0.60, 0.99)
Chow (2003)[36]	Cohort study	262 hemodialysis and peritoneal dialysis patients receiving dialysis at Monash Medical Center (Australia) on 05/31/1996	Baseline beta blocker use versus non-use was not associated with all-cause mortality - The corresponding HR was not presented
Abbott (2004)[68]	Cohort study	2,250 incident hemodialysis and peritoneal dialysis patients enrolled in the USRDS Morbidity and Mortality Study Wave 2 study who were Medicare eligible at study enrollment in 1996	Baseline beta blocker use versus non-use was associated with ↓ occurrence of the a composite end-point of CV death or hospitalized heart failure - HR (95% CI) = 0.77 (0.61, 0.97)
Ishani (2004)[69]	Cohort study	3,044 incident hemodialysis or peritoneal dialysis patients enrolled in the USRDS Morbidity and Mortality Study Wave 2 study who were Medicare eligible at study enrollment in 1996 and 1997	Baseline beta blocker use versus non-use was not significantly associated with the composite outcome of all-cause death or a CV event (MI, stroke, heart failure or PVD) - HR (95% CI) = 0.95 (0.85, 1.06)
Winkelmayer (2006)[70]	Cohort study	902 elderly dialysis patients hospitalized for MI who survived 90 days after discharge and who were enrolled in Medicare, and PAAD or PACE	Beta blocker use versus non-use during the first 90 days after discharge for acute MI was not associated with all-cause death - HR (95% CI) = 1.05 (0.78, 1.43)
Pun (2007)[71]	Nested case-control study	729 hemodialysis patients treated at a Gambro Facility between 2002 to 2005 who experienced cardiac arrest	Beta blocker use versus non-use at the time of cardiac arrest was associated with ↓ all-cause death after cardiac arrest - OR (95% CI) = 0.32 (0.17, 0.61)
Lopes (2009)[29]	Cohort study	17,350 hemodialysis patients enrolled in DOPPS I and II	Baseline beta blocker use versus non-use was associated with ↓ all-cause death

			- HR = 0.87 (95% CI were not presented)
Nakao (2009)[72]	Cohort study	2,286 hemodialysis patients enrolled in DOPPS II from Japan	Baseline beta blocker use versus non-use was associated with ↓ all-cause mortality - HR (95% CI) = 0.48 (0.25, 0.88)
Tangri (2011)[73]	Cohort study	1,747 hemodialysis patients enrolled in the HEMO Study	Baseline beta blocker use versus non-use was not significantly associated with sudden cardiac death among those with and without ischemic heart disease - With: HR (95% CI) = 0.65 (0.42-1.01) - Without: HR (95% CI) = 1.61 (0.92-2.80)
Kitchlu (2012)[74]	Cohort study	1,836 elderly, incident hemodialysis patients from Ontario, Canada who initiated maintenance dialysis therapy between 07/1991 and 07/2007 who were new users of a study drug of interest - Defined as filling least 2 prescriptions for a beta blocker, calcium channel blocker or a statin between 60 to 120 days apart	New beta blocker use versus new statin use was not associated with all-cause mortality - HR (95% CI) = 1.07 (0.92, 1.23) New use of a high dose beta blocker versus a low dose was associated with ↓ all cause mortality - HR (95% CI) = 0.50 (0.29, 0.88)
Matsue (2013)[75]	Cohort study	306 hemodialysis patients treated at Kameda Medical Center (Japan) from 2005 - 2006	Baseline beta blocker use versus non-use was associated with ↓ sudden cardiac death - HR (95%) = 0.21 (0.06, 0.69)
Tang (2015)[76]	Ecologic study	50,468 incident hemodialysis patients dually eligible for Medicare and Medicaid from 2000 – 2005	Zip codes with a higher than expected use of beta blockers (area treatment ratio > 1) versus those with lower than expected use had ↓ rates of all-cause mortality - β = -0.161, p = 0.02

[a] Adjusted results are presented.

Abbreviations: CI, confidence interval; CV, cardiovascular; DOPPS, Dialysis Outcome Practice Patterns Study; HEMO Study, Hemodialysis Study; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio; PAAD, Pharmaceutical Assistance to the Aged and Disabled program in New Jersey; PACE, Pharmaceutical Contract for the Elderly in Pennsylvania; PVD, peripheral vascular disease; USRDS, United States Renal Data System.

CHAPTER 3: AN OVERVIEW OF RESEARCH METHODS

Overview

This section provides an overview of the study methods and analytic approaches used in this dissertation. Detailed research methods for each respective dissertation aim are presented in Chapters 4, 5 and 6. This project was approved by the University of North Carolina at Chapel Hill Institutional Review Board (#15-2651). A waiver of consent was granted due to the study's large size, data anonymity, and retrospective nature. All statistical analyses were preformed using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

Data source

The data source for this dissertation was a linked database containing information on over 500,000 patients with ESRD that was created by merging data from the clinical research database of a large U.S. dialysis provider (DaVita Healthcare Partners, Inc.) with the U.S. Renal Data System (USRDS) at the patient level.

DaVita Clinical Research database

DaVita HealthCare Partners Inc. is the second largest dialysis provider in the U.S. and owns over 1,500 outpatient dialysis clinics located across the country. Their database captures detailed clinical, laboratory, and treatment data on patients receiving hemodialysis treatments at their facilities. Demographic information is documented at the time of admission to a DaVita facility by unit personnel. Comorbid conditions are routinely assessed and updated by attending nephrologists and are based on patient interview, examination and medical record review.

Laboratory data are measured at the time of admission to a DaVita dialysis unit and then biweekly or monthly thereafter. Hemodialysis treatment parameters are recorded on a treatment-to-treatment basis.

United States Renal Data System database

The USRDS is a national data system that collects, analyzes and distributes information about the treatment of ESRD in the United States. The USRDS data include: the Medical Evidence Report Form (a patient history form completed upon enrollment into the Medicare ESRD program), the Medicare Enrollment database (a repository of Medicare beneficiary enrollment and entitlement data), the ESRD Death Notification Form (the official form for reporting deaths of ESRD patients) and Medicare standard analytic files (final action administrative claims data including Medicare Parts A, B and D).

Aim 1 methods (patterns of beta blocker use)

Understanding the patterns of medication use after therapy initiation is critical in comparative effectiveness/safety studies of chronic disease medications. Sustained medication efficacy depends on continual drug exposure. The occurrence of clinical outcomes and adverse events are often contingent on longitudinal drug exposure (i.e. time on therapy, and current therapy utilization). Prior studies evaluating beta blocker prescription patterns assessed medication use at a single time-point. Thus, Aim 1 was an investigation of the long-term beta blocker utilization patterns in the hemodialysis population to: 1A) determine which beta blocker subtypes (e.g. non-selective, cardioselective, and alpha beta blockers) and generic products are most commonly initiated; 1B) estimate the cumulative incidence of beta blocker discontinuation and switching after beta blocker initiation, overall, and among carvedilol and metoprolol initiators (separately); 1C) estimate the cumulative incidence of beta blocker re-initiation after beta blocker discontinuation,

overall, and among carvedilol and metoprolol discontinuers (separately). The findings from Aim 1 analyses enabled us to gain a thorough understanding of the dynamic nature of beta blocker utilization and informed the designs of Aims 2 and 3 of this dissertation.

Study population and design

Aim 1A (beta blocker initiation) and Aim 1B (beta blocker discontinuation and switching)

We conducted a retrospective cohort study using a new-user design.[77] We describe the most commonly initiated beta blocker sub-classes and generic products in the hemodialysis population. We also estimate the 1-year cumulative incidence of beta blocker discontinuation and switching among individuals receiving maintenance hemodialysis. First, using Medicare Part D claims, we identified dialysis patients treated at the large dialysis organization who initiated oral beta blocker therapy (acebutolol, atenolol, betexolol, bisoprolol, carvedilol, labetalol, metoprolol, propranolol, pindolol, nadolol, nebivolol, sotalol, timolol) from January 1, 2007 to December 30, 2012 following a 180-day baseline period free of any documented oral beta blocker use (i.e. a washout period). We then applied the following exclusion criteria: 1) age < 18 years old at the start of the baseline period, 2) dialysis vintage ≤ 90 days at the start of the baseline period, 3) lack of continuous Medicare Part A, B and D coverage during the baseline period, 4) receipt of home hemodialysis or peritoneal dialysis during the baseline period, 5) receipt of < 6 center-based hemodialysis treatments in the last 30 days of the baseline period, 6) receipt of hospice care during the baseline period, and 7) missing demographic or baseline laboratory data. In analyses considering carvedilol and metoprolol initiators (termed the sub-cohort), patients who initiated a beta blocker other than carvedilol or metoprolol were excluded. Thus, the full study cohort consisted of prevalent, adult hemodialysis patients who were new-users of any beta blocker (used

in overall beta blocker use assessments), and the sub-cohort was restricted to carvedilol and metoprolol new-users (used in assessments of carvedilol and metoprolol use).

Aim 1C (beta blocker re-initiation)

In full cohort analyses, the 180-day cumulative incidence of beta blocker re-initiation was assessed in patients who discontinued any beta blocker medication. In sub-cohort analyses, the 180-day cumulative incidence of blocker re-initiation was assessed in patients who discontinued carvedilol or metoprolol.

Exposure

In Aim 1A we classified beta blocker initiators by subtype, including non-selective beta blockers (propranolol, pindolol, nadolol, sotalol, timolol), cardioselective beta blockers (acebutolol, atenolol, betexolol, bisoprolol, metoprolol, nebivolol) and alpha-beta blockers (carvedilol, labetalol), and also described the proportion beta blocker new-users who initiated each respective generic product.

In Aims 1B (discontinuation and switching) and 1C (re-initiation), the exposure of interest was initiation any beta blocker (including all non-selective, cardioselective and alpha-beta blockers) in overall analyses, and carvedilol or metoprolol initiation in sub-cohort analyses.

Outcomes

Longitudinal beta blocker utilization was assessed by tracking Medicare Part D prescription claims post-index date. We only considered the first occurrence of each outcome during follow-up.

Discontinuation

In the full study cohort, we assessed the 1-year beta blocker discontinuation rate (i.e. a gap in beta blocker therapy). In these analyses, we were concerned with assessing continuous use of

any beta blocker medication, regardless of switching between individual agents. Discontinuation event occurred when the days supply of beta blocker therapy post-index date was exhausted for greater than the specified grace period (i.e. 30, 60 or 90 days) without subsequent dispensing of any beta blocker. The end of the specified grace period was considered the discontinuation date.

In the sub-cohort, we assessed 1-year rates of carvedilol and metoprolol discontinuation (separately). A patient was classified as a discontinuer when the days supply of their index beta blocker was exhausted for greater than the specified grace period (i.e. 30, 60 or 90 days) without a subsequent dispensing of the same medication.

For all discontinuation analyses, we determine discontinuation dates using two different analytic approaches: 1) using Medicare Part D prescription claims only (ignoring time periods spent in the hospital or skilled nursing facility), and 2) assuming patients remained beta blocker therapy during hospital and skilled nursing facility admissions. The latter approach used both prescription claims and Medicare Part A/B claims (to identify inpatient hospital and skilled nursing facility admissions).

Switching

The 1-year rate of beta blocker switching was only considered in the sub-cohort of carvedilol or metoprolol initiators. A switching event was defined as changing beta blocker medications during follow-up (i.e. the patient fills a prescription for a non-index beta blocker) A patient was considered at risk for a switching event during times of continuous medication use, including the specified grace periods. A switching event that occurred after a treatment gap was not considered. Carvedilol initiators were classified as switchers if they filled a prescription for a beta blocker other than carvedilol during follow-up. Metoprolol initiators were classified as

switchers if they filled a prescription for a beta blocker other than metoprolol during follow-up. The date of switching was assigned as the date of the non-index beta blocker fill.

Re-initiation

A re-initiation event could only occur in patients who discontinued therapy due to a gap in beta blocker treatment (defined above). A patient was at risk to re-initiate once, after the first discontinuation event. In overall analyses, re-initiation was defined as the presence of a prescription claim for any beta blocker following the first episode of beta blocker of discontinuation in the full study cohort. In sub-cohort analyses, re-initiation was defined as the presence of a prescription claim for any beta blocker following the first episode of carvedilol or metoprolol discontinuation.

Baseline covariates

Baseline covariates, including patient demographics, comorbid conditions, laboratory data, dialysis treatment parameters, and prescription medication use, were obtained during the 180-day baseline period prior to beta blocker initiation using both USRDS and large dialysis organization data.

Censoring events

Aim 1B (beta blocker discontinuation and switching) and Aim 1C (beta blocker re-initiation)

Censoring events included: kidney transplantation, dialysis modality change (to peritoneal or home hemodialysis); recovery of renal function; loss of Medicare Part A, B or D coverage; being lost to follow-up; reaching 1-year of follow-up after the index date for discontinuation and switching analyses, and reaching in 180-days of follow-up after the discontinuation date for re-initiation analyses; or study end (December 31, 2012).

Competing risks

Aim 1B (beta blocker discontinuation and switching)

In full cohort of all beta blocker initiators, all-cause death was treated as a competing risk in analyses when assessing beta blocker discontinuation. In the sub-cohort of carvedilol and metoprolol initiators: 1) all-cause death and index beta blocker switching were considered competing events when assessing index carvedilol and metoprolol discontinuation; and 2) all-cause death and index beta blocker discontinuation were considered competing events when assessing beta blocker switching.

Aim 1C (beta blocker re-initiation)

In the cohort of patients who discontinued any index beta blocker medication, all-cause death was treated as a competing risk. In the sub-cohort of patients who discontinued index carvedilol and metoprolol therapy, all-cause death and re-initiation of a non-index beta blocker were treated as competing risks.

Statistical analysis

Baseline characteristics of the full study cohort and in the sub-cohort of carvedilol and metoprolol initiators (separately) were presented to characterize the study populations of interest. Categorical variables were presented as count (%) and continuous variables were presented as mean ± standard deviation. The crude 1-year cumulative incidence of therapy discontinuation, and switching, accounting for applicable competing risks (specified above), was estimated. Individuals were followed forward in historical time from the index date to the first occurrence of a study outcome, censoring event or competing event (when applicable). The crude 180-day cumulative incidence of beta blocker re-initiation was estimated. Study patients were followed forward in

historical time starting on the day immediately following the discontinuation date until the first occurrence of beta blocker re-initiation, a censoring event or a competing event (when applicable).

Aim 2 methods (beta blocker adherence and mortality)

Non-adherence to prescription medications leads to poor outcomes, including increased adverse event rates, suboptimal long-term clinical outcomes, as well as higher healthcare utilization and costs.[78, 79] Administrative claims data are often used to evaluate and study medication adherence across wide range of patient populations.[42, 43] One of the most common claims-based adherence metrics is the proportion of days covered, or PDC. Typically, PDC is calculated using prescription pharmacy claims data by adding the number of days that a patient has medication available to them (based on the date a prescription was dispensed and its days supply) during a set period of observation, divided by the number of days in the observation period. This standard PDC calculation approach ignores time periods spent in hospital or a skilled nursing facility. In these settings, chronic disease medications, such as beta blockers, are provided to patients by hospital inpatient or skilled nursing facility pharmacies. Prescription insurance-based home medication supplies obtained from community pharmacies are not utilized. Thus, in populations with high rates of hospital and skilled nursing facility admissions (e.g. hemodialysis patients), the standard PDC metric may misestimate the time patients have chronic disease medications available to them. In Aim 2 we examined the association between beta blocker adherence (PDC $\geq$ 80%) versus non-adherence (PDC < 80%), and all-cause mortality when the: 1A) PDC was computed using standard methods (i.e. using administrative pharmacy claims only); and 2B) PDC was computed using modified methods (i.e. using administrative pharmacy claims and also accounting for time periods when patients were admitted to the hospital or a skilled nursing facility using Medicare Par A/B claims). This applied methods study will highlight the

potential importance of computing a modified-version of the PDC (i.e. accounting for time spent in the hospital or a skilled in PDC calculations) when evaluating medication adherence—mortality associations in populations that experience high rates of hospital and/or skilled nursing facility admissions (e.g. hemodialysis patients).

Study design and population

We used a retrospective cohort design with a 180-day baseline period, 180-day exposure assessment period and 1-year follow-up period to study the association between beta blocker adherence versus non-adherence and all-cause mortality among individuals receiving maintenance hemodialysis. First, using Medicare Part D claims, we identified dialysis patients treated at the large dialysis organization who initiated oral beta blocker therapy (acebutolol, atenolol, betexolol, bisoprolol, carvedilol, labetalol, metoprolol, propranolol, pindolol, nadolol, nebivolol, sotalol, timolol) from January 1, 2007 to December 30, 2012 following a 180-day baseline period free of any documented oral beta blocker use (i.e. a washout period). We then applied the following exclusion criteria: 1) age < 18 years old at the start of the baseline period, 2) dialysis vintage ≤ 90 days at the start of the baseline period, 3) lack of continuous Medicare Part A, B and D coverage during the baseline and exposure periods, 4) receipt of home hemodialysis or peritoneal dialysis during the baseline or exposure periods, 5) receipt of < 6 center-based hemodialysis treatments in the last 30 days of the baseline period, 6) receipt of hospice care during the baseline or exposure periods, 7) missing demographic or baseline laboratory data, and 8) experiencing death or a censoring event during the exposure period. Thus, the study cohort consisted of prevalent, adult hemodialysis patients who did not experience a censoring event and survived the 180-day exposure assessment period.

Study exposure, outcome and covariates

The exposure of interest, beta blocker adherence (PDC ≥ 80%) versus non-adherence (PDC <80%) was determined during the 180-day exposure assessment period using two different methodologies, a standard approach (using only Medicare Part D prescription claims data) and a modified approach (using Medicare Part D prescription claims data and Medicare Part A/B data to account for time periods where were admitted to the hospital or a skilled nursing facility). Under both paradigms, PDC was computed at the patient level as the: [number of days in the in the exposure period where a beta blocker was available / 180 days] x 100%, and was then dichotomized at the 80% high adherence threshold.

The study outcome of interest was 1-year all-cause mortality and was defined as death due to any cause. Dates of death were ascertained from the USRDS Patients file. This data file contains information derived from ESRD Death Notification Form (Centers for Medicare & Medicaid Services (CMS) Form 2746, the official form for reporting ESRD patient deaths to CMS).

Baseline covariates, including patient demographics, comorbid conditions, laboratory data, dialysis treatment parameters, and prescription medication use, were obtained during the 180-day baseline period prior to beta blocker initiation using both USRDS and large dialysis organization data.

Censoring events

Censoring events included: kidney transplantation, dialysis modality change (to peritoneal or home hemodialysis), recovery of renal function, loss of Medicare Part A, B or D coverage, being lost to follow-up, reaching 1-year of follow-up post-exposure period, or study end (December 31, 2012).

Statistical analysis

Baseline characteristics were described by adherence group (for both standard and modified PDC) as count (%) for categorical variables and mean ± standard deviation for continuous variables. In primary analyses, multivariable Cox proportional hazards regression models were used to examine the association between beta blocker adherence (PDC > 80%) versus non-adherence (PDC < 80%) and 1-year all-cause mortality when: 1) PDC was computed using standard methods, and 2) PDC was computed using modified methods (accounting for inpatient hospital and skilled nursing facility admissions). Patients were followed forward in historical time starting on the day immediately following the end of the exposure assessment period to the first occurrence of a study outcome or censoring event. Several sensitivity analyses were conducted to assess the robustness of our primary study findings.

Aim 3 methods (comparative study of carvedilol versus metoprolol initiation and mortality)

Pharmacologic and pharmacokinetic differences between carvedilol and metoprolol may alter their medication safety and efficacy profiles in the setting of ESRD. Pharmacologically, carvedilol and metoprolol differ with respect to their beta-adrenergic receptor selectivity and vasodilatory capabilities. Kinetically, physiochemical factors, such as molecular size, hydrophilicity, plasma protein binding, and volume of distribution influence the extent of carvedilol and metoprolol clearance by the hemodialysis procedure. These key factors may plausibly alter the hemodynamic and antiarrhythmic risk-benefit profiles of carvedilol and metoprolol therapy in the setting of ESRD. In Aim 3 we evaluate the association between carvedilol versus metoprolol initiation and 1-year all-cause and cardiovascular mortality, overall and within clinically relevant subgroups (including patients with: hypertension, atrial fibrillation,

heart failure, and a recent myocardial infraction). The results from this study will provide much needed information to guide carvedilol and metoprolol prescribing in the hemodialysis population.

Study design and population

We conducted a retrospective cohort study using a new-user design[77] to investigate the association between carvedilol versus metoprolol initiation and 1-year all-cause and cardiovascular mortality (separately) among individuals receiving maintenance hemodialysis. First, using Medicare Part D claims, we identified dialysis patients treated at the large dialysis organization who initiated oral beta blocker therapy (acebutolol, atenolol, betexolol, bisoprolol, carvedilol, labetalol, metoprolol, propranolol, pindolol, nadolol, nebivolol, sotalol, timolol) from January 1, 2007 to December 30, 2012 following a 180-day baseline period free of any documented oral beta blocker use (i.e. a washout period). We then applied the following exclusion criteria: 1) age < 18 years old at the start of the baseline period, 2) dialysis vintage ≤ 90 days at the start of the baseline period, 3) lack of continuous Medicare Part A, B and D coverage during the baseline period, 4) receipt of home hemodialysis or peritoneal dialysis during the baseline period, 5) receipt of < 6 center-based hemodialysis treatments in the last 30 days of the baseline period, 6) receipt of hospice care during the baseline period, 7) missing demographic or laboratory data, and 8) initiation of a beta blocker other than carvedilol or metoprolol. Thus, the study cohort consisted of prevalent, adult hemodialysis patients who were carvedilol or metoprolol new-users.

Exposure, outcome and covariates

The exposures of interest were carvedilol and metoprolol initiation. The index date was designated as the date of the first carvedilol or metoprolol prescription after the baseline period.

Study outcomes of interest were 1-year all-cause and cardiovascular mortality (assessed separately). All-cause mortality was defined as death due to any cause. Cardiovascular mortality

was defined death due to: acute myocardial infarction, pericarditis, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, pulmonary edema due to exogenous fluid, congestive heart failure, pulmonary embolus or stroke. Dates of death and cause of death information were ascertained from the USRDS Patients file. This data file contains information derived from the ESRD Death Notification Form (CMS Form 2746, the official form for reporting ESRD patient deaths to CMS).

Baseline covariates, including patient demographics, comorbid conditions, laboratory data, dialysis treatment parameters, and prescription medication use, were obtained during the 180-day baseline period prior to beta blocker initiation using both USRDS and large dialysis organization data.

Subgroups

Subgroups of interest included individuals with the main cardiovascular indications for beta blocker therapy: hypertension, atrial fibrillation, heart failure, and a recent myocardial infarction. Subgroup classifications were determined based upon patients' baseline comorbid status using International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes obtained from USRDS Medicare Part A/B data.

Censoring events

Censoring events included: kidney transplantation, dialysis modality change (to peritoneal or home hemodialysis), recovery of renal function, loss of Medicare Part A, B or D coverage, being lost to follow-up, reaching 1-year of follow-up post-exposure period, or study end (December 31, 2012).

Statistical analysis

Baseline characteristics were described across carvedilol and metoprolol initiators as count (%) for categorical variables and mean ± standard deviation for continuous variables. Baseline covariate distributions were compared using standardized differences. A standardized difference >0.1 represents meaningful imbalance between treatment groups.[80]

In primary analyses, we used an intent-to-treat approach to evaluate the association between carvedilol (versus metoprolol) initiation and 1-year all-cause and cardiovascular mortality. Cox proportional hazards models were used to assess the study medication—all-cause mortality association. Fine and Gray proportional subdistribution hazards models[81] that treated non-cardiovascular death as a competing risk were used to assess the study medication—cardiovascular mortality association. Both models estimate HRs and their 95% CIs. Inverse probability of treatment (IPT) weighting was used to control for confounding. We used multivariable logistic regression to calculate the predicted probability (i.e. propensity score) of receiving carvedilol (versus metoprolol) as a function of baseline covariates. Propensity scores were used to generate IPT weights.[82] We estimated adjusted HRs by applying IPT weights in regression models. In addition, several sensitivity analyses were performed to assess the robustness of our primary study results. We also conducted a *post hoc* analysis to evaluate potential mechanistic explanations for our study findings.

CHAPTER 4: RESULTS AIM 1

Introduction

Understanding the patterns of medication use after therapy initiation is critical in comparative effectiveness/safety studies of chronic disease medications. Sustained medication efficacy depends on continual drug exposure. The occurrence of clinical outcomes and adverse events are often contingent on longitudinal drug exposure (i.e. time on therapy and current therapy utilization). The majority of epidemiologic studies evaluating beta blocker utilization in the hemodialysis population have been cross-sectional in nature, and evaluated the beta blocker class as a whole, and provide little, if any information on the utilization patterns of beta blocker subclasses or individual agents.[5, 28-41] In a cohort of maintenance hemodialysis patients initiating beta blocker therapy we describe: 1) which beta blocker subtypes (e.g. non-selective, cardioselective, and alpha beta blockers) and generic products are the most commonly initiated, and 2) the longitudinal beta blocker utilization patterns, including discontinuation, switching and re-initiation.

Methods

Data source

The study data were extracted from the clinical database of a large U. S. dialysis organization and the USRDS. Data were linked at the patient level. The dialysis organization operates over 1,500 outpatient dialysis clinics throughout the nation. Its database captures detailed demographic, clinical, laboratory, and dialysis treatment data. Laboratory data are measured on a

biweekly or monthly basis. Hemodialysis treatment parameters are recorded on a treatment-to-treatment basis. The USRDS is a national ESRD surveillance system that includes: the Medical Evidence and ESRD Death Notification forms, the Medicare Enrollment database (a repository of Medicare beneficiary enrollment and entitlement data), and Medicare standard analytic files (final action administrative claims data including Medicare Parts A, B and D).

Study population and design

Beta blocker discontinuation and switching

We conducted a retrospective cohort study using a new-user design.[77] We describe the most commonly initiated beta blocker sub-classes and generic products in the hemodialysis population. We also estimate the 1-year cumulative incidence of beta blocker discontinuation and switching among individuals receiving maintenance hemodialysis (**Figure 4.1**). First, using Medicare Part D claims, we identified dialysis patients treated at the large dialysis organization who initiated oral beta blocker therapy (acebutolol, atenolol, betexolol, bisoprolol, carvedilol, labetalol, metoprolol, propranolol, pindolol, nadolol, nebivolol, sotalol, timolol) from January 1, 2007 to December 30, 2012 following a 180-day washout period free of any documented oral beta blocker use. We then applied the following exclusion criteria: 1) age < 18 years old at the start of the baseline period, 2) dialysis vintage ≤ 90 days at the start of the baseline period, 3) lack of continuous Medicare Part A, B and D coverage during the baseline period, 4) receipt of home hemodialysis or peritoneal dialysis during the baseline period, 5) receipt of < 6 center-based hemodialysis treatments in the last 30 days of the baseline period, 6) receipt of hospice care during the baseline period, and 7) missing demographic or baseline laboratory data. In analyses considering carvedilol and metoprolol initiators (termed the sub-cohort), patients who initiated a beta blocker other than carvedilol or metoprolol were excluded. Thus, the full study cohort consisted of prevalent, adult

hemodialysis patients who were new-users of any beta blocker (used in overall beta blocker use assessments), and the sub-cohort was restricted to carvedilol and metoprolol new-users (used in assessments of carvedilol and metoprolol use).

Beta blocker re-initiation

In full cohort analyses, the 180-day cumulative incidence of beta blocker re-initiation was assessed in patients who discontinued any beta blocker medication. In sub-cohort analyses, the 180-day cumulative incidence of blocker re-initiation was assessed in patients who discontinued carvedilol or metoprolol. Study designs for re-initiation analyses are depicted in **Figure 4.2**.

Exposure

In analyses characterizing beta blocker initiation, beta blocker initiators were classified by: 1) subtype, including non-selective beta blockers (propranolol, pindolol, nadolol, sotalol, timolol), cardioselective beta blockers (acebutolol, atenolol, betexolol, bisoprolol, metoprolol, nebivolol) and alpha-beta blockers (carvedilol, labetalol), and 2) and individual generic products.

When assessing beta blocker discontinuation, switching and re-initiation, the exposure of interest was initiation any beta blocker in overall analyses (including all non-selective, cardioselective and alpha-beta blockers), and carvedilol or metoprolol initiation in sub-cohort analyses.

Outcomes

Longitudinal beta blocker utilization was assessed by tracking Medicare Part D prescription claims post-index date. We only considered the first occurrence of each outcome during follow-up.

Discontinuation

In the full study cohort (all beta blocker initiators), we assessed the 1-year rate of beta blocker discontinuation (i.e. a gap in beta blocker therapy). In these analyses, we were interested in assessing continuous use of any beta blocker medication. In these analyses switching between individual agents within the beta blocker class was allowed. A discontinuation event occurred when the days supply of beta blocker therapy post-index date was exhausted for greater than the specified grace period (i.e. 30, 60 or 90 days) without subsequent dispensing of any beta blocker. The end of the specified grace period was considered the discontinuation date. An example of beta blocker discontinuation is illustrated in **Panel A of Figure 4.3**.

In the sub-cohort (carvedilol and metoprolol initiators only), we assessed 1-year carvedilol and metoprolol discontinuation (separately). A patient was classified as a discontinuer when the days supply of the index beta blocker was exhausted for greater than the specified grace period (i.e. 30, 60 or 90 days) without a subsequent dispensing of the same medication.

For all discontinuation analyses, we determined discontinuation dates using two different analytic approaches: 1) using Medicare part D prescription claims only, and 2) using Medicare D claims and Medicare Part A/B claims to account for time periods that patients spent in the hospital or a skilled nursing facility. The latter expanded claims-based approach facilitated the identification of inpatient hospital and skilled nursing facility admissions. In these analyses, we assumed that patients remained on beta blocker therapy during hospital and skilled nursing facility admissions. **Figure 4.4** depicts how the beta blocker days supply values were adjusted for hospital and skilled nursing facility admissions.

Switching

The 1-year cumulative incidence of beta blocker switching was only considered in the sub-cohort of carvedilol or metoprolol initiators. A switching event was defined as changing beta blocker medications during follow-up (i.e. the patient fills a prescription for a non-index beta blocker). A patient was considered at risk for a switching event during times of continuous medication use, including the specified grace periods. A switching event that occurred after a treatment gap was not considered. Carvedilol initiators were classified as switchers if they filled a prescription for a beta blocker other than carvedilol during follow-up. Metoprolol initiators were classified as switchers if they filled a prescription for a beta blocker other than metoprolol during follow-up. The date of switching was assigned as the date of the non-index beta blocker fill. An example of beta blocker switching is illustrated in **Panel B of Figure 4.3**.

Re-initiation

A re-initiation event could only occur in patients who discontinued therapy due to a gap in beta blocker treatment (defined above). A patient was at risk to re-initiate once, after the first discontinuation event. In overall analyses, re-initiation was defined as the presence of a prescription claim for any beta blocker following the first episode of beta blocker of discontinuation in the full study cohort. In sub-cohort analyses, re-initiation was defined as the presence of a prescription claim for any beta blocker following the first episode of carvedilol or metoprolol discontinuation. An depiction of beta blocker re-initiation is illustrated in **Panel C of Figure 4.3**.

Baseline covariates

Baseline covariates, including patient demographics, comorbid conditions, laboratory data, dialysis treatment parameters, and prescription medication use, were obtained during the 180-day

baseline period prior to beta blocker initiation using both USRDS and large dialysis organization data (**Appendix: Supplemental Table 1**).

Censoring events

In all analyses, censoring events included: 1) kidney transplantation, 2) dialysis modality change (to peritoneal or home hemodialysis), 3) recovery of renal function, 4) loss of Medicare Part A, B or D coverage, 5) being lost to follow-up, 6) reaching 1-year of follow-up after the index date for discontinuation and switching analyses and reaching in 180-days of follow-up after the discontinuation date for re-initiation analyses, or 7) study end (December 31, 2012).

Competing risks

A competing risk is an event that either hinders the observation of the event of interest or modifies the chance that this event occurs.

Beta blocker discontinuation and switching

In the full cohort (all beta blocker initiators) all-cause death was treated as a competing risk in analyses when assessing beta blocker discontinuation. In the sub-cohort of carvedilol and metoprolol initiators: 1) all-cause death and index beta blocker switching were considered competing events when assessing index carvedilol and metoprolol discontinuation; and 2) all-cause death and index beta blocker discontinuation were considered competing events when assessing beta blocker switching.

Beta blocker re-initiation

In the cohort of patients who discontinued any index beta blocker medication, all-cause death was treated as a competing risk. In the sub-cohort of patients who discontinued index carvedilol or metoprolol therapy, all-cause death and re-initiation of a non-index beta blocker were treated as competing risks.

Statistical analysis

Baseline characteristics of the full study cohort and the sub-cohort were presented to characterize the main study populations. Categorical variables are presented as count (%) and continuous variables are presented as mean ± standard deviation. The crude 1-year cumulative incidence of therapy discontinuation, and switching, accounting for applicable competing risks (specified above) was estimated. Individuals were followed forward in historical time from the index date to the first occurrence of a study outcome, censoring event or competing event (when applicable). The crude 180-day cumulative incidence of beta blocker re-initiation was estimated. Study patients were followed forward in historical time starting on the day immediately following the discontinuation date until the first occurrence of beta blocker re-initiation, a censoring event or a competing event (when applicable).

Results

Assessment of beta blocker initiation

Figure 4.5 displays a flow diagram of the study cohort selection. A total of 33,888 hemodialysis patients initiated beta blocker therapy between 2007 and 2012, including 477 (1.4%) non-selective beta blocker, 20,764 (61.3%) cardioselective and 12,643 (37.3%) beta blocker initiators (**Table 4.1**). Overall, metoprolol (51.6%) and carvedilol (28.2%) were the most commonly initiated agents. Baseline characteristics for the full study cohort (all beta blocker initiators) and the sub-cohort (carvedilol and metoprolol initiators) are presented in **Table 4.2**. Both cohorts are similar to the broader U.S. hemodialysis population with respect to age, sex and cause of ESRD.[48]

Overall assessment of beta blocker discontinuation and re-initiation

When assessing the beta blocker class as a whole, the 1-year cumulative incidence of therapy cessation post-index date was common, ranging from 40.1% to 68.5% depending on the discontinuation definition employed (**Table 4.3**). In particular, rates of beta blocker discontinuation were the highest when a 30-day grace period was used to define therapy cessation, and were the lowest when a 90-day grace period was used. Regardless of the grace period used to define discontinuation, making the assumption that patients continued beta blocker therapy during hospital and skilled nursing facility admissions resulted in slightly lower estimates 1-year beta blocker discontinuation as compared to discontinuation estimates based upon prescription fill data alone (**Table 4.3**, **Figure 4.6**). Furthermore, re-initiation of beta blocker therapy, after a treatment gap, also occurred frequently (**Table 4.4, Figure 4.7**). The 180-day cumulative incidence of restarting any blocker beta medication ranged from 45.7% to 63.4%.

Assessment of carvedilol and metoprolol discontinuation, switching and re-initiation

Similar to overall analyses, carvedilol and metoprolol discontinuation were common (**Table 4.5**, **Figure 4.8**). Depending on definition, discontinuation ranged from 35.0% to 64.7% among carvedilol initiators, and ranged from 39.2% to 66.3% among metoprolol initiators. Switching to a non-index beta blocker was uncommon, and occurred at similar rates among carvedilol and metoprolol initiators (**Table 4.6**, **Figure 4.9**). Index beta blocker re-initiation was slightly higher among carvedilol discontinuers as compared to metoprolol discontinuers after their initial therapy lapse (**Table 4.7**, **Figure 4.10**).

Implications for subsequent dissertation aims

Dissertation aim 2

We found that 1-year beta blocker therapy cessation post-index date (i.e. discontinuation from the beta blocker class as a whole) was common. Rates of 180-day beta blocker re-initiation after an initial treatment gap we high. Based on these findings beta blocker utilization post-index date in this cohort of maintenance hemodialysis patients was dynamic. Thus, a study assessing beta blocker adherence and mortality (i.e. Aim 2 of this dissertation) will be feasible. Notably, regardless of the grace period used to define discontinuation, making the assumption that patients continued beta blocker therapy during hospital and skilled nursing facility admissions resulted in slightly lower estimates of 1-year beta blocker discontinuation as compared to discontinuation estimates based upon prescription fill data alone. These findings suggest that administrative claims-based studies assessing beta blocker (or any chronic medication) adherence in the hemodialysis population should consider accounting for hospital and skilled nursing facility admissions when longitudinally tracking beta blocker (or any chronic medication) utilization as a means to estimate medication adherence.

Dissertation Aim 3

Carvedilol and metoprolol were the most commonly initiated beta blockers (79.7% of all beta blocker new-users). Since, these beta blockers have similar indication profiles in the setting of ESRD a comparative study evaluating the association between carvedilol and metoprolol initiation and mortality among individuals receiving maintenance hemodialysis (i.e. Aim 3 of this dissertation) will likely be feasible and of high clinical interest. Even though carvedilol and metoprolol therapy cessation was common, we found that a high proportion of carvedilol and metoprolol discontinuers re-initiated on their index beta blocker medication. Furthermore, among carvedilol and metoprolol initiators respectively, switching to a non-index beta blocker was

uncommon. These findings suggest that after the initial carvedilol or metoprolol prescription, patients tend to remain on their index beta blocker even after gaps in therapy. Thus, when assessing the association between carvedilol and metoprolol initiation and mortality, an appropriate primary analytic approach will be analyzing data using an intent-to-treat paradigm.

Tables

Table 4.1 Frequency of beta blocker initiation by subclass and generic product

Beta blocker subclass and generic product	n (%)
Non-selective	**477 (1.4%)**
Propranolol	309 (0.9%)
Nadolol	84 (0.3%)
Other[a]	84 (0.3%)
Cardioselective	**20,764 (61.3%)**
Metoprolol	17,506 (51.6%)
Metoprolol tartrate	*11,736 (34.6%)*
Metoprolol succinate	*5,770 (17.0%)*
Atenolol	2,805 (8.3%)
Nebivolol	352 (1.0%)
Other[b]	105 (0.3%)
Alpha-beta	**12,643 (37.3%)**
Carvedilol	9,558 (28.2%)
Labetalol	3,085 (9.1%)

There were a total of 33,888 beta blocker initiators identified.

[a] Other non-selective beta blockers include: sotalol, pindolol, timolol

[b] Other cardioselective beta blockers include: bisoprolol, acebutolol, betaxolol

Table 4.2 Characteristics of the Aim 1 full study cohort and sub-cohort

Characteristic	Full study cohort n = 33,888	Sub-cohort n = 27,064
Age (years)	58.7 ± 15.0	59.6 ± 14.7
Female	15,835 (46.7%)	12,630 (46.7%)
Race		
White	16,961 (50.1%)	13,902 (51.4%)
Black	15,015 (44.3%)	11,605 (42.9%)
Other	1,912 (5.6%)	1,557 (5.8%)
Hispanic ethnicity	6,580 (19.4%)	5,276 (19.5%)
Low-income subsidy	26,238 (77.4%)	20,783 (76.8%)
Year index beta blocker was prescribed		
2007	6,109 (18.0%)	4,703 (17.4%)
2008	5,631 (16.6%)	4,396 (16.2%)
2009	5,085 (15.0%)	4,001 (14.8%)
2010	5,291 (15.6%)	4,220 (15.6%)
2011	5,658 (16.7%)	4,656 (17.2%)
2012	6,114 (18.0%)	5,088 (18.8%)
Cause of ESRD		
Diabetes	15,846 (46.8%)	13,254 (49.0%)
Hypertension	9,893 (29.2%)	7,614 (28.1%)
Glomerular disease	3,818 (11.3%)	2,845 (10.5%)
Other	4,331 (12.8%)	3,351 (12.4%)
Body mass index		
< 18.5 kg/m^2	1,643 (4.8%)	1,318 (4.9%)
18.5 – 24.9 kg/m^2	12,485 (36.8%)	9,840 (36.4%)
25.0 – 29.9 kg/m^2	9,709 (28.7%)	7,739 (28.6%)
≥ 30.0 kg/m^2	10,051 (29.7%)	8,167 (30.2%)
History of prior renal transplant	2,366 (7.0%)	1,706 (6.3%)
Dialysis vintage		
< 1.0 year	1,849 (5.5%)	1,530 (5.7%)
1.0 – 1.9 years	7,110 (21.0%)	5,823 (21.5%)
2.0 – 2.9 years	5,528 (16.3%)	4,446 (16.4%)
$\geq$ 3.0 years	19,401 (57.3%)	15,265 (56.4%)
Atrial fibrillation	4,188 (12.4%)	3,761 (13.9%)
Other arrhythmia	2,909 (8.6%)	2,560 (9.5%)
Angina	595 (1.8%)	512 (1.9%)
Cancer	1,183 (3.5%)	973 (3.6%)
Conduction disorder	965 (2.8%)	863 (3.2%)
COPD/asthma	5,299 (15.6%)	4,499 (16.6%)
Coronary atherosclerosis	9,132 (26.9%)	8,086 (29.9%)
Diabetes	17,601 (51.9%)	14,759 (54.5%)
GI bleed	1,730 (5.1%)	1,403 (5.2%)

Heart failure	10,745 (31.7%)	9,358 (34.6%)
Hypertension	23,994 (70.8%)	19,673 (72.7%)
Liver disease	1,593 (4.7%)	1,204 (4.4%)
Myocardial infarction	1,921 (5.7%)	1,793 (6.6%)
Peripheral artery disease	6,891 (20.3%)	5,878 (21.7%)
Stroke	3,397 (10.0%)	2,851 (10.5%)
Valvular disease	2,555 (7.5%)	2,241 (8.3%)
History of non-compliance[a]	2,002 (5.9%)	1,615 (6.0%)
Vascular access		
Fistula	19,786 (58.4%)	15,699 (58.0%)
Graft	8,616 (25.4%)	6,879 (25.4%)
Catheter	5,486 (16.2%)	4,486 (16.6%)
Interdialytic weight gain ≥ 3 kg	8,379 (24.7%)	6,573 (24.3%)
Delivered dialysis treatment time < 240 min	27,074 (79.9%)	21,597 (79.8%)
Pre-dialysis systolic BP		
< 130 mmHg	4,090 (12.1%)	3,543 (13.1%)
130 – 149 mmHg	9,076 (26.8%)	7,440 (27.5%)
150 – 169 mmHg	11,815 (34.9%)	9,259 (34.2%)
≥170 mmHg	8,907 (26.3%)	6,822 (25.2%)
Recent history of intradialytic hypotension[b]	4,317 (12.7%)	3,712 (13.7%)
Albumin		
≤ 3.0 g/dL	1,617 (4.8%)	1,351 (5.0%)
3.1 – 4.0 g/dL	21,115 (62.3%)	17,278 (63.8%)
> 4.0 g/dL	11,156 (32.9%)	8,435 (31.2%)
Calcium		
< 8.5 mg/dL	4,866 (14.4%)	3,835 (14.2%)
8.5 – 10.2 mg/dL	4,866 (14.4%)	21,915 (81.0%)
> 10.2 mg/dL	1,633 (4.8%)	1,314 (4.9%)
Phosphorus		
< 3.5 mg/dL	3,628 (10.7%)	2,995 (11.1%)
3.5 – 5.5 mg/dL	18,169 (53.6%)	14,655 (54.1%)
> 5.5 mg/dL	12,091 (35.7%)	9,414 (34.8%)
Potassium		
< 4.0 mEq/L	3,698 (10.9%)	2,982 (11.0%)
4.0 – 6.0 mEq/L	28,896 (85.3%)	23,067 (85.2%)
> 6.0 mEq/L	1,294 (3.8%)	1,015 (3.8%)
Hemoglobin		
< 9.5 g/dL	2,229 (6.6%)	1,829 (6.8%)
9.5 – 12.0 mg/dL	20,963 (61.9%)	16,873 (62.3%)
> 12.0 mg/dL	10,696 (31.6%)	8,362 (30.9%)
Equilibrated Kt/V < 1.2		6,085 (22.5%)

Number of medications in last 30 days of baseline	5.4 ± 3.9	5.5 ± 3.9
Alpha blocker	302 (0.9%)	231 (0.9%)
ACE inhibitor	7,865 (23.2%)	6,272 (23.2%)
Angiotensin receptor blocker	3,911 (11.5%)	3,060 (11.3%)
Calcium channel blocker	11,638 (34.3%)	9,019 (33.3%)
Central alpha agonist	5,149 (15.2%)	3,758 (13.9%)
Diuretic	3,720 (11.0%)	3,084 (11.4%)
Vasodilator	3,833 (11.3%)	2,913 (10.8%)
Statin	8,451 (24.9%)	7,087 (26.2%)
Other cholesterol medication[c]	1,355 (4.0%)	1,111 (4.1%)
Digoxin	673 (2.0%)	590 (2.2%)
Long-acting nitrate	2,389 (7.0%)	2,061 (7.6%)
Antiplatelet medication	3,907 (11.5%)	3,345 (12.4%)
Anticoagulant medication	2,535 (7.5%)	2,169 (8.0%)
Midodrine	605 (1.8%)	542 (2.0%)

All-covariates were measured during the baseline period prior to beta blocker initiation. Values for categorical variables are given as number (%) and as mean ± standard deviation for continuous variables.

[a] Claims-based definition of non-compliance included ICD-9 discharge diagnosis codes V15.81 (personal history of noncompliance with medical treatment, presenting hazards to health) and V45.12 (noncompliance with renal dialysis).

[b] Patients were considered as having a recent history of intradialytic hypotension if they had an intradialytic nadir systolic blood pressure < 90 mmHg in at least 30% of outpatient hemodialysis treatments in the last 30 days of the baseline period.[57]

[c] Other cholesterol medications included the following non-statin cholesterol medications: bile acid sequestrants, cholesterol absorption inhibitors, fibrates and niacin.

Abbreviations: ACE, angiotensin converting enzyme; BP, blood pressure; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; GI, gastrointestinal; ICD-9, International Classification of Diseases, Ninth Revision.

Table 4.3 1-year cumulative incidence of beta blocker discontinuation

Grace period use to determine discontinuation	1-year cumulative incidence
30 days	
Rx claims only	68.5%
Rx claims adjusted for admissions	63.7%
60 days	
Rx claims only	53.6%
Rx claims adjusted for admissions	50.0%
90 days	
Rx claims only	42.7%
Rx claims adjusted for admissions	40.1%

This table presents the 1-year cumulative incidence of beta blocker discontinuation in the full study cohort (n = 33,888) when a discontinuation event was defined using a 30, 60 and 90-day grace periods. Within each of these grace periods, we describe the 1-year cumulative incidence of discontinuation: 1) using prescription claims only (Rx claims only); and 2) using prescription claims + Medicare Part A/B claims (to identify inpatient hospital and skilled nursing facility admissions), making the assumption that patients remained beta blocker therapy during hospital and skilled nursing facility admissions (Rx claims adjusted for admissions). All-cause death was treated as a competing risk.

Abbreviations: Rx, prescription.

Table 4.4 180-day cumulative incidence of beta blocker re-initiation among beta blocker discontinuers

Grace period used to determine beta blocker discontinuation[a]	Cohort size[a]	180-day cumulative incidence
30 days		
Rx claims only	20,832	63.4%
Rx claims adjusted for admissions	19,341	62.4%
60 days		
Rx claims only	15,818	54.1%
Rx claims adjusted for admissions	14,742	53.1%
90 days		
Rx claims only	12,280	46.5%
Rx claims adjusted for admissions	11,548	45.7%

This table presents the 180-day cumulative incidence of beta blocker re-initiation in the among 6 different cohorts of beta blocker discontinuers. All-cause death was treated as a competing risk.

[a] The size of each of these cohorts was contingent on the definition that was used to define beta blocker discontinuation post-index date. Discontinuation was defined using 30, 60 and 90-day grace periods. Within each of these grace periods, 1-year cumulative incidence of discontinuation was determined: 1) using prescription claims only (Rx claims only); and 2) using prescription claims + Medicare Part A/B claims (to identify inpatient hospital and skilled nursing facility admissions), making the assumption that patients remained beta blocker therapy during hospital and skilled nursing facility admissions (Rx claims adjusted for admissions).

Abbreviations: Rx, prescription.

Table 4.5 1-year cumulative incidence of carvedilol and metoprolol discontinuation

Grace period used to determine discontinuation	1-year cumulative incidence	
	Carvedilol n = 9,558	**Metoprolol n = 17,506**
30 days		
Rx claims only	64.7%	66.3%
Rx claims adjusted for admissions	59.6%	61.3%
60 days		
Rx claims only	48.8%	52.0%
Rx claims adjusted for admissions	45.1%	48.6%
90 days		
Rx claims only	37.9%	41.5%
Rx claims adjusted for admissions	35.0%	39.2%

This table presents the 1-year cumulative incidence of beta blocker discontinuation in the sub-cohort of carvedilol and metoprolol initiators (n=27,064). Carvedilol and metoprolol discontinuation were considered separately. A Discontinuation was defined using 30, 60 and 90-day grace periods. Within each of these grace periods, we describe the 1-year cumulative incidence of discontinuation: 1) using prescription claims only (Rx claims only); and 2) using prescription claims + Medicare Part A/B claims (to identify inpatient hospital and skilled nursing facility admissions), making the assumption that patients remained beta blocker therapy during hospital and skilled nursing facility admissions (Rx claims adjusted for admissions). All-cause death and switching to an non-index beta blocker were treated as competing risks.

Abbreviations: Rx, prescription.

Table 4.6 1-year cumulative incidence of switching to a non-index beta blocker among carvedilol and metoprolol initiators

Grace period used to determine discontinuation[a]	1-year cumulative incidence	
	Carvedilol n = 9,558	**Metoprolol n = 17,506**
30 days		
Rx claims only	5.0%	5.2%
Rx claims adjusted for admissions	5.5%	5.6%
60 days		
Rx claims only	6.3%	6.7%
Rx claims adjusted for admissions	6.6%	6.9%
90 days		
Rx claims only	7.1%	7.7%
Rx claims adjusted for admissions	7.4%	7.8%

This table presents the 1-year cumulative incidence of switching to a non-index beta blocker discontinuation in the sub-cohort of carvedilol and metoprolol initiators (n=27,064). Carvedilol and metoprolol switching were considered separately. All-cause death and index beta blocker discontinuation were treated as a competing risk.

[a] Index beta blocker discontinuation (a competing risk in these analyses) was defined using a 30, 60 and 90-day grace periods. Within each of these grace periods, 1-year cumulative incidence of discontinuation was determined: 1) using prescription claims only (Rx claims only); and 2) using prescription claims + Medicare Part A/B claims (to identify inpatient hospital and skilled nursing facility admissions), making the assumption that patients remained beta blocker therapy during hospital and skilled nursing facility admissions (Rx claims adjusted for admissions).

Abbreviations: Rx, prescription.

Table 4.7 180-day cumulative incidence of index beta blocker re-initiation among individuals who were index carvedilol and metoprolol discontinuers

Grace period used to determine index beta blocker discontinuation[a]	Cohort size[a]	180-day cumulative incidence	
		Carvedilol	Metoprolol
30 days			
Rx claims only	15,915	62.0%	58.0%
Rx claims adjusted for admissions	14,692	61.3%	57.1%
60 days			
Rx claims only	11,960	51.9%	48.5%
Rx claims adjusted for admissions	11,110	50.6%	47.4%
90 days			
Rx claims only	9,028	43.6%	40.2%
Rx claims adjusted for admissions	8,645	42.7%	39.4%

This table presents the 180-day cumulative incidence of beta blocker re-initiation among 6 different sub-cohorts of carvedilol and metoprolol discontinuers. All-cause death was treated as a competing risk.

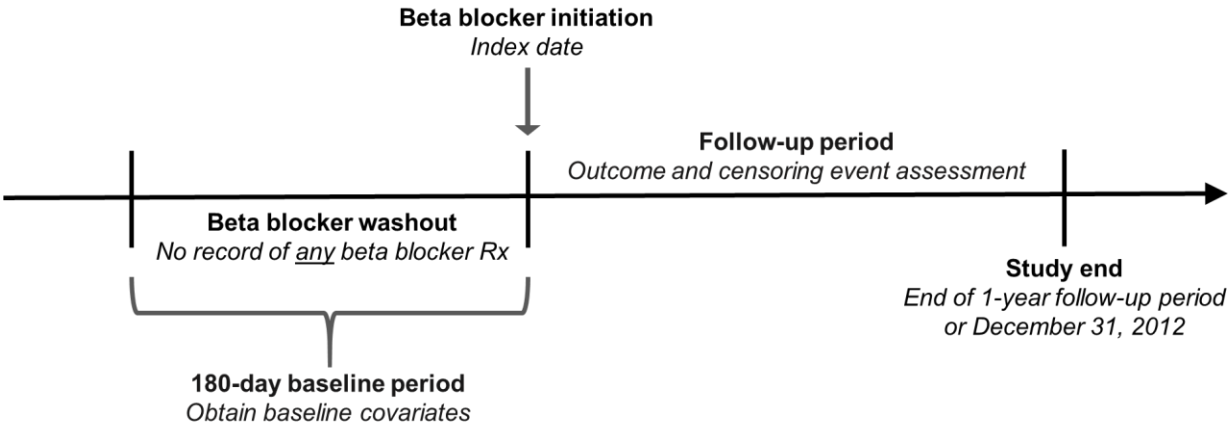
[a] The size of each of these cohorts was contingent on the definition that was used to define beta blocker discontinuation post-index date. Discontinuation was defined using a 30, 60 and 90-day grace periods. Within each of these grace periods, 1-year cumulative incidence od discontinuation was determined: 1) using prescription claims only (Rx claims only); and 2) using prescription claims + Medicare Part A/B claims (to identify inpatient hospital and skilled nursing facility admissions), making the assumption that patients remained beta blocker therapy during hospital and skilled nursing facility admissions (Rx claims adjusted for admissions).

Abbreviations: Rx, prescription.

Figures

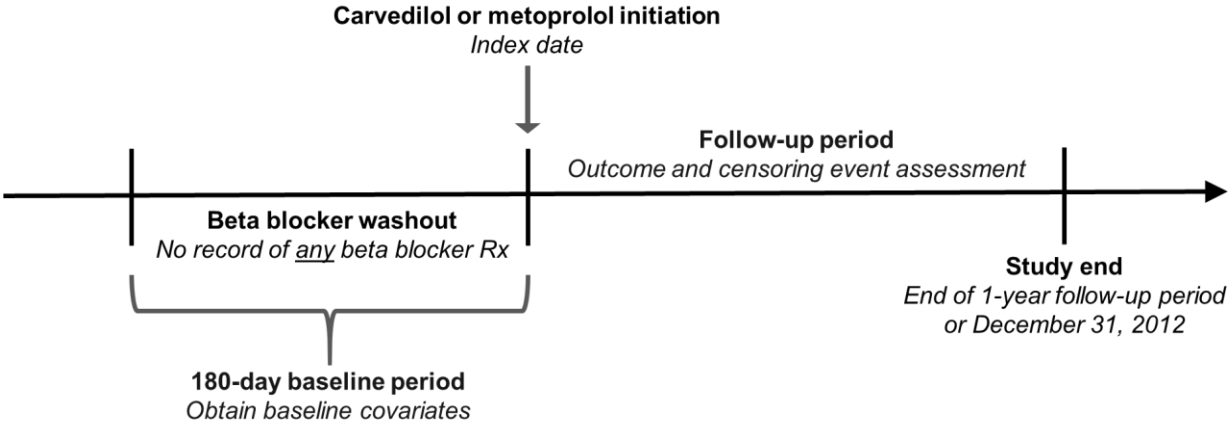
Figure 4.1 Aim 1 study designs for discontinuation and switching analyses

Panel A. Full cohort (includes all beta blocker initiators)



Beta blocker initiators were defined as hemodialysis patients who had no record of a beta blocker prescription in the previous 180 days (beta blocker washout period). Among these patients, the index date was defined as the date of beta blocker initiation. Baseline covariates were identified in the 180-day period prior to the index date. Study follow-up began immediately after the index date.

Panel B. Sub-cohort study (includes carvedilol and metoprolol initiators only)

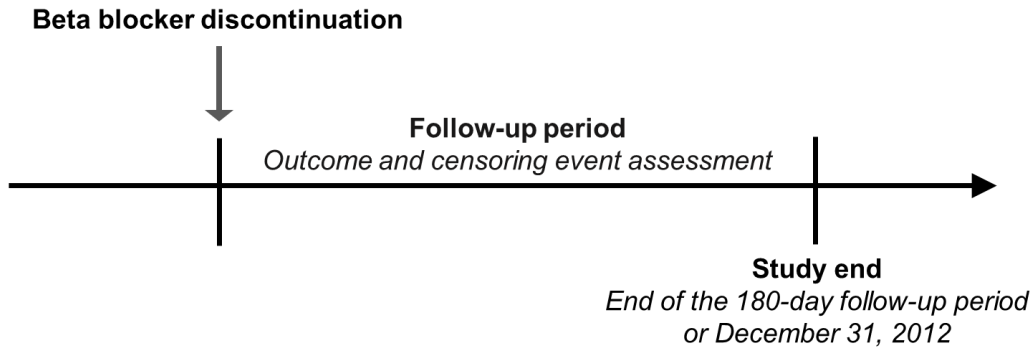


Carvedilol and metoprolol initiators were defined as hemodialysis patients who had no record of a beta blocker prescription in the previous 180 days (beta blocker washout period). Among these patients, the index date was defined as the date of carvedilol or metoprolol initiation. Baseline covariates were identified in the 180-day period prior to the index date. Study follow-up began immediately after the index date.

Abbreviations: Rx, prescription.

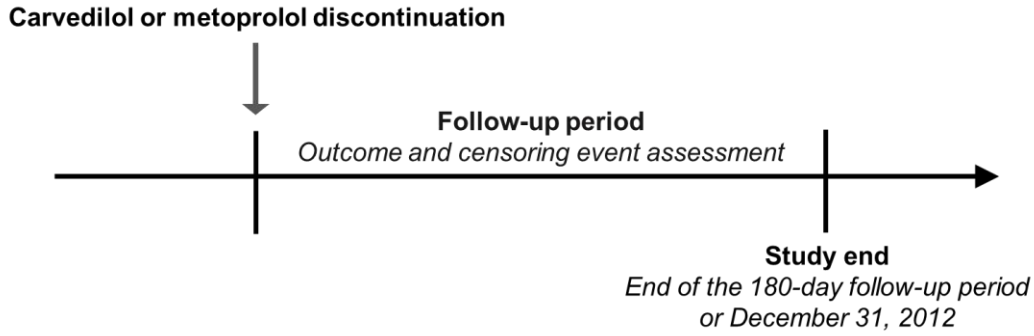
Figure 4.2 Aim 1 study designs for re-initiation analyses

Panel A. Full cohort (includes all beta blocker discontinuers)



Beta blocker discontinuation occurred when the days supply of beta blocker therapy post-index date was exhausted for greater than a specified grace period (i.e. 30, 60 or 90 days) without subsequent dispensing of any beta blocker. The end of the specified grace period was considered the discontinuation date. Study follow-up began immediately after the discontinuation date.

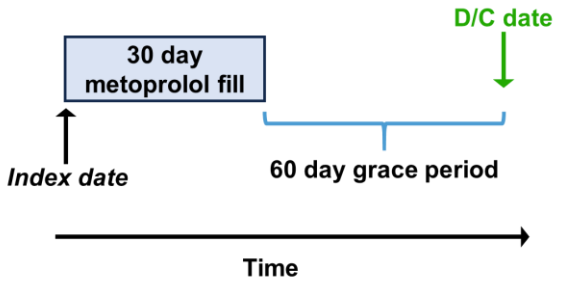
Panel B. Sub-cohort study (includes carvedilol and metoprolol discontinuers only)



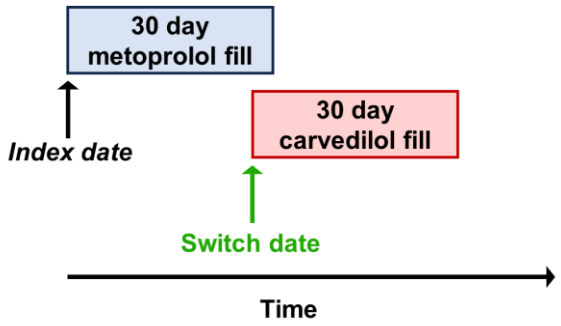
Carvedilol and metoprolol discontinuation was assessed separately. A patient was classified as a discontinuer when the days supply of the index beta blocker was exhausted for greater than the specified grace period (i.e. 30, 60 or 90 days) without a subsequent dispensing of the same medication. The end of the specified grace period was considered the discontinuation date. Study follow-up began immediately after the discontinuation date.

Figure 4.3 Illustrative examples of beta blocker discontinuation, switching and re-initiation

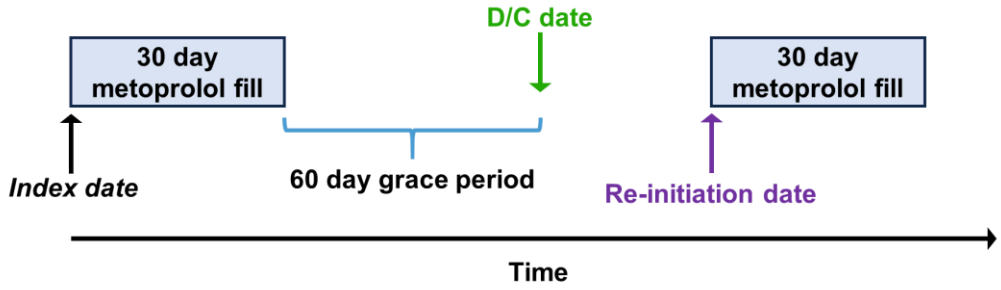
Panel A. Discontinuation



Panel B. Switching

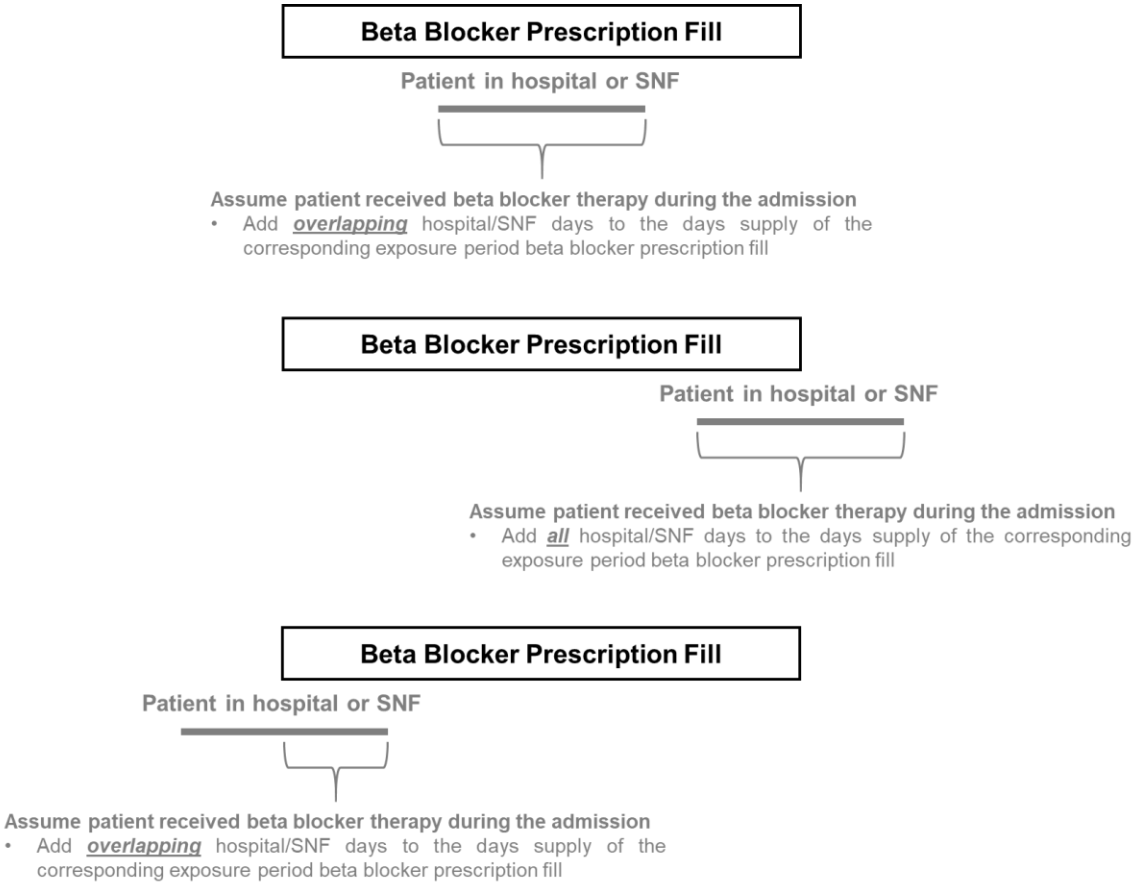


Panel C. Re-initiation



Abbreviations: D/C, discontinuation.

Figure 4.4 Illustration of beta blocker days supply adjustment made when patients were admitted to the hospital or skilled nursing facility in Aim 1 analyses



Abbreviations: SNF, skilled nursing facility.

Figure 4.5 Flow diagram depicting the assembly of the Aim 1 study cohorts

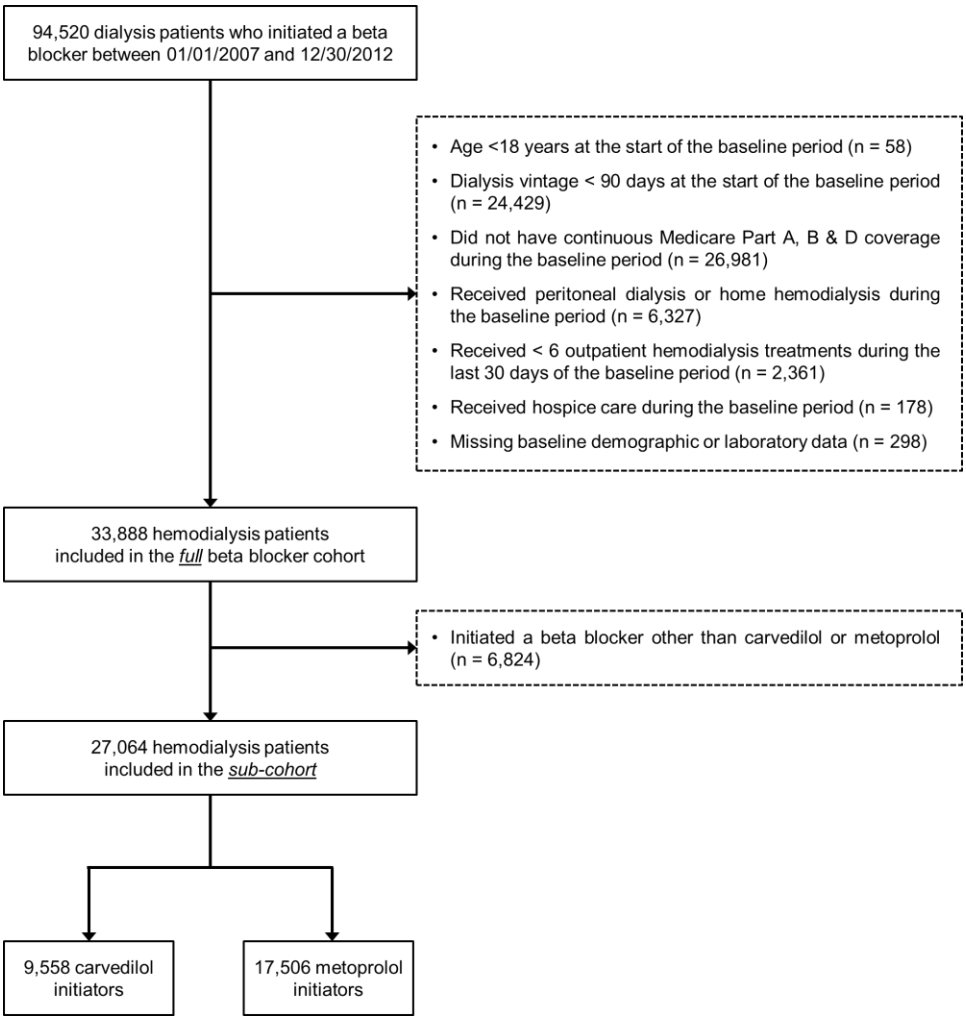
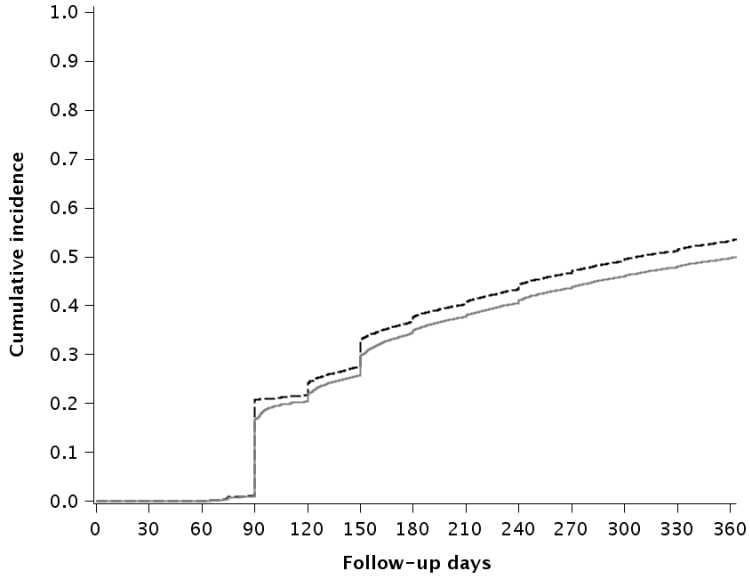
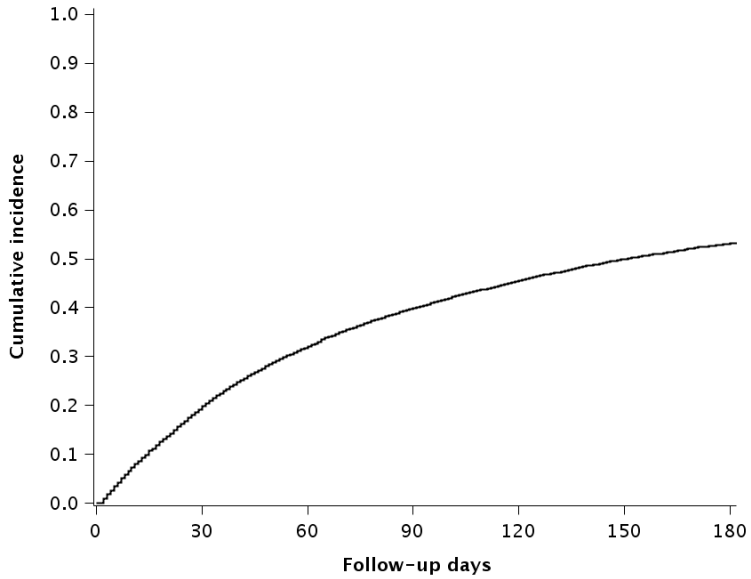


Figure 4.6 A representative plot of the 1-year cumulative incidence of beta blocker therapy discontinuation



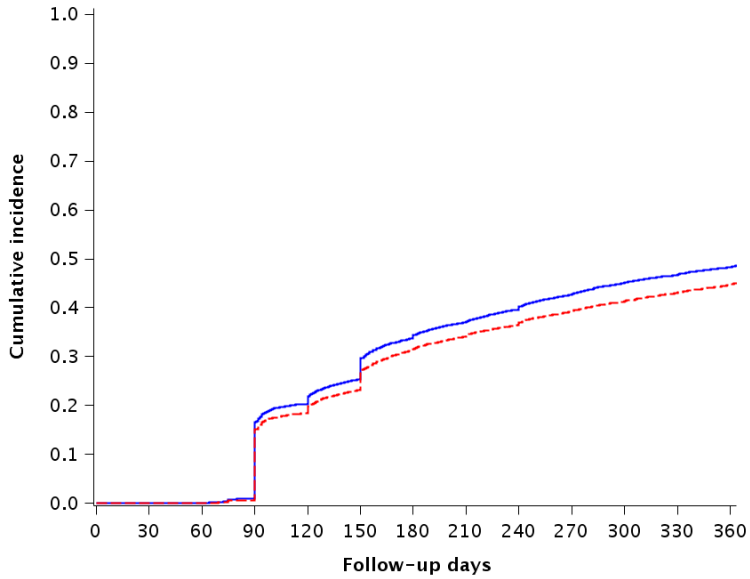
This plot illustrates the 1-year cumulative incidence of beta blocker discontinuation in the full study cohort (n = 33,888) when a discontinuation event was defined using a 60-day grace period. The black dashed line represents the 1-year cumulative incidence of discontinuation when therapy cessation was determined using prescription claims only; the gray solid line represents the 1-year cumulative incidence of discontinuation when therapy cessation was determined using prescription claims + Medicare Part A/B claims (to identify inpatient hospital and skilled nursing facility admissions), making the assumption that patients remained beta blocker therapy during hospital and skilled nursing facility admissions. All-cause death was treated as a competing risk.

Figure 4.7 A representative plot of the 180-day cumulative incidence of beta blocker re-initiation



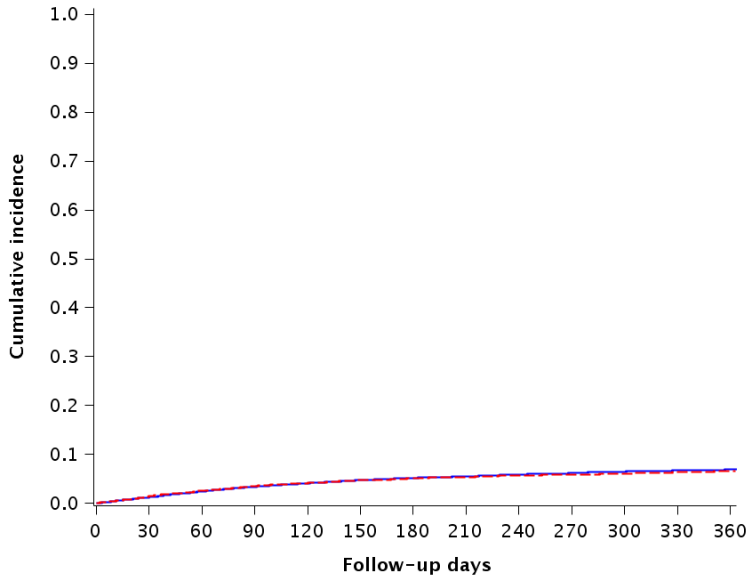
This plot illustrates the 1-year cumulative incidence of beta blocker re-initiation among beta blocker discontinuers (n = 14,742) when: 1) a discontinuation event was defined using a 60-day grace period; and 2) assuming patients continued index beta blocker therapy during applicable hospital and skilled nursing facility admissions. All-cause death was treated as a competing risk.

Figure 4.8 A representative plot of the 1-year cumulative incidence of carvedilol and metoprolol discontinuation



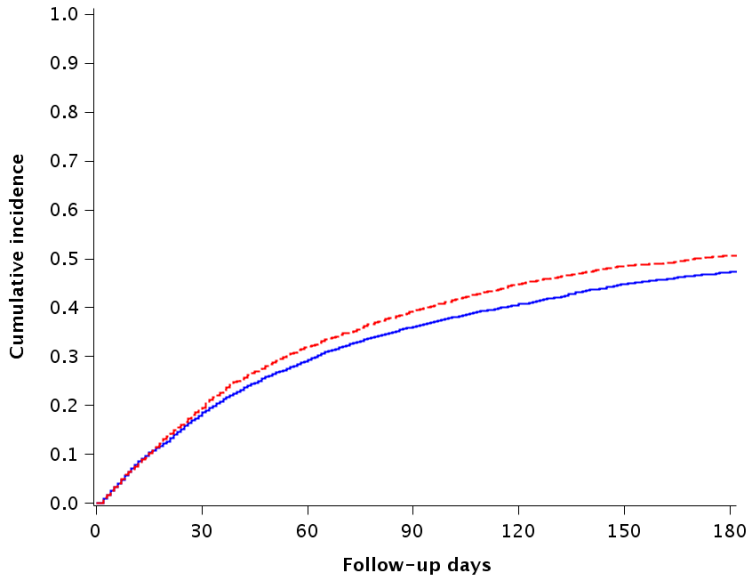
This plot illustrates the 1-year cumulative incidence of beta blocker discontinuation in the sub-cohort of carvedilol and metoprolol initiators (n = 27,064) when 1) a discontinuation event was defined using a 60-day grace period and 2) assuming patients continued index beta blocker therapy during applicable hospital and skilled nursing facility admissions. The red dashed lines represent the 1-year cumulative incidence of carvedilol discontinuation and the blue solid lines represent the 1-year cumulative incidence of metoprolol discontinuation. All-cause death and switching to a non-index beta blocker were treated as competing risks.

Figure 4.9 A representative plot of the 1-year cumulative incidence of carvedilol and metoprolol switching



This plot illustrates the 1-year cumulative incidence of carvedilol and metoprolol switching (assessed separately) in the sub-cohort of carvedilol and metoprolol initiators (n = 27,064) when: 1) a discontinuation event was defined using a 60-day grace period; and 2) assuming patients continued index beta blocker therapy during applicable hospital and skilled nursing facility admissions. The red dashed lines represent the 1-year cumulative incidence of switching to a non-carvedilol beta blocker during follow-up among carvedilol initiators. The blue solid line represents the 1-year cumulative incidence of switching to a non-metoprolol beta blocker during follow-up among metoprolol initiators. All-cause death and index beta blocker discontinuation were treated as competing risks.

Figure 4.10 A representative plot the 1-year cumulative incidence of carvedilol and metoprolol re-initiation



In this plot, the hemodialysis patient cohort eligible for re-initiation analyses included 11,110 individuals who discontinued index carvedilol or metoprolol therapy due to a gap in treatment of at least 60 days as determined using both Medicare Part D prescription and Medicare Part A/B hospital and skilled nursing facility claims (i.e. we assumed that patients remained beta blocker therapy during hospital and skilled nursing facility admissions). The red dashed lines represent the 180-day cumulative incidence of carvedilol re-initiation among carvedilol discontinuers. The blue solid line represents the 180-day cumulative incidence of metoprolol re-initiation metoprolol discontinuers. All-cause death and re-initiation of a non-index beta blocker were treated as competing risks.

CHAPTER 5: RESULTS AIM 2

Introduction

Non-adherence to prescription medications leads to poor outcomes, including increased adverse event rates, suboptimal long-term clinical outcomes, as well as higher healthcare utilization and costs.[78, 79] Administrative claims data are often used to evaluate and study medication adherence across wide range of patient populations, including individuals with kidney disease.[42, 43] One of the most common claims-based adherence metrics is the proportion of days covered, or PDC. Typically, the PDC is calculated using pharmacy claims data by adding the number of days that a patient has prescription medication available to them (based on the date a prescription was dispensed and its days supply) during a set period of observation, and dividing this sum by the number of total days in the observation period. This standard approach for the calculation of PDC ignores time periods spent in hospital or a skilled nursing facility. In these settings, chronic disease medications, such as beta blockers, are provided to patients by hospital inpatient or skilled nursing facility pharmacies. Typically, patients do not use prescription insurance-based home medication supplies obtained from community pharmacies during hospital or skilled nursing facility. Thus, in populations with high rates of hospital and skilled nursing facility admissions (e.g. hemodialysis patients), the standard PDC metric may misestimate the time patients have chronic disease medications available to them. In a cohort of hemodialysis patients newly initiating beta blocker therapy, we examine the association between beta blocker adherence (PDC $\geq$ 80%) versus non-adherence (PDC < 80%) and all-cause mortality when the: 1) PDC is computed using standard methods (i.e. using administrative pharmacy claims only); and 2) PDC

is computed using modified methods (i.e. using administrative pharmacy claims and also accounting for time periods patients spent the hospital or a skilled nursing facility using Medicare Part A/B claims).

Methods

Data source

The study data were extracted from the clinical database of a large U. S. dialysis organization and the USRDS. Data were linked at the patient level. The dialysis organization operates over 1,500 outpatient dialysis clinics throughout the nation. Its database captures detailed demographic, clinical, laboratory, and dialysis treatment data. Laboratory data are measured on a biweekly or monthly basis. Hemodialysis treatment parameters are recorded on a treatment-to-treatment basis. The USRDS is a national ESRD surveillance system that includes: the Medical Evidence and ESRD Death Notification forms, the Medicare Enrollment database (a repository of Medicare beneficiary enrollment and entitlement data), and Medicare standard analytic files (final action administrative claims data including Medicare Parts A, B and D).

Study design and population

We used a retrospective cohort design with a 180-day baseline period, 180-day exposure assessment period and 1-year follow-up period to study the association between beta blocker adherence and all-cause mortality among individuals receiving maintenance hemodialysis (**Figure 5.1**). First, using Medicare Part D claims, we identified dialysis patients treated at the large dialysis organization who initiated oral beta blocker therapy (acebutolol, atenolol, betexolol, bisoprolol, carvedilol, labetalol, metoprolol, propranolol, pindolol, nadolol, nebivolol, sotalol, timolol) from January 1, 2007 to December 30, 2012 following a 180-day washout period free of any documented oral beta blocker use. We then applied the following exclusion criteria: 1) age < 18

years old at the start of the baseline period, 2) dialysis vintage ≤ 90 days at the start of the baseline period, 3) lack of continuous Medicare Part A, B and D coverage during the baseline and exposure periods, 4) receipt of home hemodialysis or peritoneal dialysis during the baseline or exposure periods, 5) receipt of < 6 center-based hemodialysis treatments in the last 30 days of the baseline period, 6) receipt of hospice care during the baseline or exposure periods, 7) missing demographic or baseline laboratory data, and 8) experiencing death or a censoring event during the exposure period. Thus, the study cohort consisted of prevalent, adult hemodialysis patients who did not experience a censoring event and survived the 180-day exposure assessment period.

Study exposure, outcome and covariates

The exposure of interest, beta blocker adherence (PDC ≥ 80%) versus non-adherence (PDC < 80%) was determined during the 180-day exposure assessment period using two different methodologies, a standard approach (using only Medicare Part D prescription claims data) and a modified approach (using Medicare Part D prescription claims data and also Medicare Part A/B data to account for time periods when patients were admitted to the hospital or a skilled nursing facility). Under both paradigms, PDC was computed at the patient level as the: [number of days in the in the exposure period where a beta blocker was available / 180 days] x 100%, and was then dichotomized at the 80% high adherence threshold. Individuals' with a PDC ≥ 80% were considered adherent, whereas individuals with a PDC < 80% were considered non-adherent.

The study outcome of interest was 1-year all-cause mortality. All-cause mortality was defined as death due to any cause. Dates of death were ascertained from the USRDS Patients file. This data file contains information derived from ESRD Death Notification Form (CMS Form 2746, the official form for reporting ESRD patient deaths to CMS).

Baseline covariates, including patient demographics, comorbid conditions, laboratory data, dialysis treatment parameters, and prescription medication use, were obtained during the 180-day baseline period prior to beta blocker initiation using both USRDS and large dialysis organization data (**Appendix: Supplemental Table 1**).

Censoring events

Censoring events included: kidney transplantation, dialysis modality change (to peritoneal or home hemodialysis), recovery of renal function, loss of Medicare Part A, B or D coverage, being lost to follow-up, reaching 1-year of follow-up post-exposure period, or study end (December 31, 2012).

Statistical analysis

Baseline characteristics were described by adherence group (for both standard and modified PDC) as count (%) for categorical variables and mean ± standard deviation for continuous variables. In primary analyses, multivariable Cox proportional hazards regression models were used to examine the association between beta blocker adherence (PDC $\geq$ 80%) versus non-adherence (PDC < 80%) and 1-year all-cause mortality when: 1) PDC was computed using standard methods, and 2) PDC was computed using modified methods (accounting for inpatient hospital and skilled nursing facility admissions). Patients were followed forward in historical time starting on the day immediately following the end of the exposure assessment period to the first occurrence of a study outcome or censoring event. We conduced sensitivity analyses to assess the robustness of our primary study findings. First, since beta blocker therapy is typically titrated at 2- to 4-week intervals, we repeated primary analyses to and restricted the study cohort to only include patients with an index beta blocker fill with a days supply of 30 days or less. Second, since Medicare Part D beneficiaries who have supplemental Medicare Part D low-income subsidy

coverage receive prescription medications at very little or no cost, these individuals may be likely to obtain medications without using their prescription insurance benefit. Thus, we repeated primary analyses in the subset of study patients with the low-income subsidy benefit.

Results

Study cohort characteristics

Figure 5.2 displays a flow diagram of study cohort selection. A total of 26,071 hemodialysis patients were included in the study. During the 180-day exposure assessment period the study cohort filled a total of 98,130 beta blocker prescriptions. A total of 13,476 (51.7%) individuals were admitted to the hospital for at least 1 exposure period day, and 2,554 (9.8%) individuals received care in a skilled nursing facility for least 1 exposure period day. Of the 98,130 exposure period beta blocker fills, 19,882 (20.2%) overlapped with a hospital and/or skilled nursing facility admission, impacting 11,282 (43.3%) of study hemodialysis patients. When PDC was computed using standard methods, the average beta blocker PDC in the study cohort was 63.9% ± 29.5%, and 10,324 (39.6%) of study patients were classified as adherent to beta blocker therapy (PDC ≥ 80%). In contrast, when PDC was computed using modified methods, the average beta blocker PDC in the study cohort was 65.8% ± 29.6%, and 11,015 (42.3%) of study patients were considered adherent to beta blocker therapy. **Table 5.1** displays the study cohort characteristics stratified by beta blocker adherence status (PDC ≥ 80% and < 80%).

Primary analyses

The study cohort was followed for a total of 20,639 person-years. During follow-up, a total of 3,855 all-cause deaths occurred. Regardless of the PDC metric used, patients who were adherent to beta blocker therapy (PDC ≥ 80%) had lower rates of all-cause mortality as compared to

individuals who were non-adherent to beta blocker therapy (PDC < 80%). However, when PDC was estimated using modified methods (as compared to standard methods) the estimated beta blocker adherence-mortality association was attenuated (**Table 5.2**).

Sensitivity analyses

Sensitivity analyses restricting the analytic cohort to individuals that had an index beta blocker fill with a days supply of 30 days or less generated results similar to primary analyses. Beta blocker adherence (versus non-adherence) was associated with lower all-cause mortality. This association was attenuated when adherence was estimated using modified (versus standard) PDC (**Table 5.3**).

Sensitivity analyses evaluating the beta blocker adherence-mortality association among individuals with the Medicare Part D low-income subsidy benefit, also produced results similar results to primary analyses. Beta blocker adherence (versus non-adherence) was associated with lower all-cause mortality. This association was attenuated when adherence was estimated using modified (versus standard) PDC (**Table 5.4**).

Discussion

In this study we evaluated the association between beta blocker adherence and all-cause mortality in a cohort of maintenance hemodialysis patients. Beta blocker adherence was estimated using a common claims-based adherence metric, the PDC. PDC was computed using two different approaches: 1) the standard method (using pharmacy claims only), and 2) a modified method (using pharmacy claims and also accounting for the time patients spent in the hospital or a skilled nursing facility). Under both approaches, we found that patients who were adherent to beta blocker therapy (PDC > 80%) as compared to those who were non-adherent (PDC < 80%) had lower rates of all-cause mortality. However, when modified (versus standard) beta blocker PDC was used to

classify patients as adherent or non-adherent, the observed adherence—mortality association was attenuated.

Individuals receiving maintained hemodialysis are at high risk for medication non-adherence, due to their tremendous comorbid disease burden which requires treatment with an average of 10 chronic disease medications.[83] Thus, accurate estimates of the longitudinal patterns of medication use across time are essential when studying medication adherence in this vulnerable patient population. To our knowledge, this is the first investigation describing medication adherence in the hemodialysis population using both standard PDC metrics and an alternative PDC-based approach that accounted for time spent in the hospital or in a skilled nursing facility. In particular, we studied beta blockers, the cardiovascular medication class most commonly prescribed to hemodialysis patients.[5, 28] When calculating the modified version of the PDC metric, we assumed that: 1) beta blockers were provided to patients by hospital inpatient or skilled nursing facility pharmacies; and 2) home medication supplies obtained from Medicare Part D-based prescription fills were not utilized during these health care encounters and accumulated for later use after hospital or skilled nursing facility discharge. The proportion of patients considered as adherent to beta blocker therapy (PDC $\geq$ 80%) was lower when the standard PDC metric was employed, indicating that the classification of patients into adherent and non-adherent categories varies depending on the PDC metric used to estimate adherence status. Thus, future studies describing medication adherence and its subsequent clinical sequelae in the hemodialysis population may need to consider multiple adherence assessment approaches to ensure that study findings are robust.

Our results should be considered in the context of study limitations. First, our study was observational, and it is possible that residual confounding may exist. Second, prescription claims

data only capture pharmacy-based medication fills that were billed to a patient's prescription drug insurance. Thus, we were unable to identify beta blocker fills that were obtained outside of the prescription drug benefit (i.e. cash prescriptions). To address this limitation, we restricted our study cohort to patients with Medicare Part D low-income subsidy benefit in sensitivity analyses. These individuals receive prescription medications at very little or no cost and are less likely to obtain prescription medications from the pharmacy using other payment methods. Reassuringly, the observed study findings from this sensitivity analysis were consistent with our primary results. Third, the dispensation of a beta blocker prescription does not guarantee that individuals are taking the medication. Data on consumption of medications are not available in prescription claims data. However, it is reasonable to assume that patients would not continue to fill and pay for prescription medications if they are not taking them regularly. Finally, we did not have information provider-based dosing and discontinuation instructions. Thus, we were not able to differentiate between a lack of adherence due beta blocker discontinuation by indication (i.e. the patient experienced a side effect warranting therapy cessation) versus self-discontinuation.

Based on the findings of this study, we conclude that adherence to beta blocker therapy is associated with lower all-cause mortality. In addition, our results suggest that it may be important to consider time periods spent in the hospital or a skilled nursing facility when computing PDC to evaluate the study medication adherence—mortality associations in populations that experience high rates of the aforementioned health care admissions (e.g. hemodialysis patients). Further research evaluating the impact of the PDC-based adherence adjustment method used in this study in non-dialysis patient populations is warranted.

Tables

Table 5.1 Baseline characteristics by beta blocker adherence category

Characteristic	Standard PDC		Modified PDC	
	PDC ≥ 80% n =10,324	PDC < 80% n = 15,747	PDC ≥ 80% n = 11,015	PDC < 80% n = 15,056
Age (years)	59.2 ±14.7	57.3 ± 14.9	59.4 ±14.7	57.1 ± 14.9
Female	4,883 (47.3%)	7,307 (46.4%)	5,263 (47.8%)	6,927 (46.0%)
Race				
White	5,395 (52.3%)	7,324 (46.5%)	5,737 (52.1%)	6,982 (46.4%)
Black	4,315 (41.8%)	7,550 (47.9%)	4,633 (42.1%)	7,232 (48.0%)
Other	614 (5.9%)	873 (5.5%)	645 (5.9%)	842 (5.6%)
Hispanic ethnicity	2,110 (20.4%)	3,086 (19.6%)	2,207 (20.0%)	2,989 (19.9%)
Low-income subsidy	8,186 (79.3%)	12,275 (78.0%)	8,769 (79.6%)	11,692 (77.7%)
Year index beta blocker was prescribed				
2007	1,644 (15.9%)	3,450 (21.9%)	1,789 (16.2%)	3,305 (22.0%)
2008	1,738 (16.8%)	2,979 (18.9%)	1,865 (16.9%)	2,852 (18.9%)
2009	1,649 (16.0%)	2,595 (16.5%)	1,768 (16.1%)	2,476 (16.4%)
2010	1,896 (18.4%)	2,566 (16.3%)	2,010 (18.2%)	2,452 (16.3%)
2011	2,170 (21.0%)	2,675 (17.0%)	2,289 (20.8%)	2,556 (17.0%)
2012	1,227 (11.9%)	1,482 (9.4%)	1,294 (11.7%)	1,415 (9.4%)
Cause of ESRD				
Diabetes	4,921 (47.7%)	7,134 (45.3%)	5,327 (48.4%)	6,728 (44.7%)
Hypertension	2,967 (28.7%)	4,652 (29.5%)	3,135 (28.5%)	4,484 (29.8%)
Glomerular disease	1,125 (10.9%)	1,891 (12.0%)	1,180 (10.7%)	1,836 (12.2%)
Other	1,311 (12.7%)	2,070 (13.1%)	1,373 (12.5%)	2,008 (13.3%)
Body mass index				
< 18.5 kg/m^2	417 (4.0%)	710 (4.5%)	459 (4.2%)	668 (4.4%)
18.5 – 24.9 kg/m^2	3,788 (36.7%)	5,689 (36.1%)	4,065 (36.9%)	5,412 (35.9%)
25.0 – 29.9 kg/m^2	2,980 (28.9%)	4,552 (28.9%)	3,158 (28.7%)	4,374 (29.1%)
≥ 30.0 kg/m^2	3,139 (30.4%)	4,796 (30.5%)	3,333 (30.3%)	4,602 (30.6%)
History of prior renal transplant	668 (6.5%)	1,218 (7.7%)	700 (6.4%)	1,186 (7.9%)
Dialysis vintage				
< 1.0 year	644 (6.2%)	848 (5.4%)	683 (6.2%)	809 (5.4%)
1.0 – 1.9 years	2,301 (22.3%)	3,184 (20.2%)	2,463 (22.4%)	3,022 (20.1%)
2.0 – 2.9 years	1,702 (16.5%)	2,530 (16.1%)	1,803 (16.4%)	2,429 (16.1%)
≥ 3.0 years	5,677 (55.0%)	9,185 (58.3%)	6,066 (55.1%)	8,796 (58.4%)
Atrial fibrillation	1,131 (11.0%)	1,623 (10.3%)	1,271 (11.5%)	1,483 (9.8%)
Other arrhythmia	791 (7.7%)	1,179 (7.5%)	881 (8.0%)	1,089 (7.2%)
Angina	155 (1.5%)	272 (1.7%)	175 (1.6%)	252 (1.7%)
Cancer	311 (3.0%)	442 (2.8%)	335 (3.0%)	418 (2.8%)
Conduction disorder	260 (2.5%)	396 (2.5%)	292 (2.7%)	364 (2.4%)
COPD/asthma	1,433 (13.9%)	2,239 (14.2%)	1,597 (14.5%)	2,075 (13.8%)
Coronary atherosclerosis	2,569 (24.9%)	3,816 (24.2%)	2,841 (25.8%)	3,544 (23.5%)

Diabetes	5,226 (50.6%)	7,651 (48.6%)	5,714 (51.9%)	7,163 (47.6%)
GI bleed	441 (4.3%)	748 (4.8%)	500 (4.5%)	689 (4.6%)
Heart failure	2,920 (28.3%)	4,724 (30.0%)	3,253 (29.5%)	4,391 (29.2%)
Hypertension	7,088 (68.7%)	11,055 (70.2%)	7,705 (70.0%)	10,438 (69.3%)
Liver disease	386 (3.7%)	728 (4.6%)	425 (3.9%)	689 (4.6%)
Myocardial infarction	522 (5.1%)	767 (4.9%)	575 (5.2%)	714 (4.7%)
Peripheral artery disease	1,861 (18.0%)	2,952 (18.7%)	2,111 (19.2%)	2,702 (17.9%)
Stroke	1,031 (10.0%)	1,343 (8.5%)	1,178 (10.7%)	1,196 (7.9%)
Valvular disease	661 (6.4%)	1,082 (6.9%)	737 (6.7%)	1,006 (6.7%)
History of non-compliance[a]	452 (4.4%)	919 (5.8%)	512 (4.6%)	859 (5.7%)
Vascular access				
Fistula	6,171 (59.8%)	9,059 (57.5%)	6,491 (58.9%)	8,739 (58.0%)
Graft	2,703 (26.2%)	4,133 (26.2%)	2,880 (26.1%)	3,956 (26.3%)
Catheter	1,450 (14.0%)	2,555 (16.2%)	1,644 (14.9%)	2,361 (15.7%)
Interdialytic weight gain ≥ 3 kg	2,491 (24.1%)	4,187 (26.6%)	2,650 (24.1%)	4,02 (26.8%)
Delivered dialysis treatment time < 240 min	8.222 (79.6%)	12,397 (78.7	8,776 (79.7%)	11,843 (78.7%)
Pre-dialysis systolic BP				
< 130 mmHg	1,019 (9.9%)	1,703 (10.8%)	1,107 (10.0%)	1,615 (10.7%)
130 – 149 mmHg	2,805 (27.2%)	4,019 (25.5%)	2,999 (27.2%)	3,825 (25.4%)
150 – 169 mmHg	3,710 (35.9%)	5,607 (35.6%)	3,949 (35.9%)	5,368 (35.7%)
≥170 mmHg	2,790 (27.0%)	4,418 (28.1%)	2,960 (26.9%)	4,248 (28.2%)
Recent history of intradialytic hypotension[b]	1,075 (10.4%)	1,907 (12.1%)	1,179 (10.7%)	1,803 (12.0%)
Albumin				
≤ 3.0 g/dL	363 (3.5%)	561 (3.6%)	440 (4.0%)	484 (3.2%)
3.1 – 4.0 g/dL	6,255 (60.6%)	9,842 (62.5%)	6,731 (61.1%)	9,366 (62.2%)
> 4.0 g/dL	3,706 (35.9%)	5,344 (33.9%)	3,844 (34.9%)	5,206 (34.6%)
Calcium				
< 8.5 mg/dL	1,428 (13.8%)	2,436 (15.5%)	1,506 (13.7%)	2,358 (15.7%)
8.5 – 10.2 mg/dL	8,488 (82.2%)	12,488 (79.3%)	9,048 (82.1%)	11,928 (79.2%)
> 10.2 mg/dL	408 (4.0%)	823 (5.2%)	461 (4.2%)	770 (5.1%)
Phosphorus				
< 3.5 mg/dL	1,146 (11.1%)	1,480 (9.4%)	1,237 (11.2%)	1,389 (9.2%)
3.5 – 5.5 mg/dL	5,887 (57.0%)	8,001 (50.8%)	6,272 (56.9%)	7,616 (50.6%)
> 5.5 mg/dL	3,291 (31.9%)	6,266 (39.8%)	3,506 (31.8%)	6,051 (40.2%)
Potassium				
< 4.0 mEq/L	1,078 (10.4%)	1,711 (10.9%)	1,149 (10.4%)	1,640 (10.9%)
4.0 – 6.0 mEq/L	8,872 (85.9%)	13,422 (85.2%)	9,453 (85.8%)	12,841 (85.3%)
> 6.0 mEq/L	374 (3.6%)	614 (3.9%)	413 (3.7%)	575 (3.8%)
Hemoglobin				
< 9.5 g/dL	600 (5.8%)	908 (5.8%)	664 (6.0%)	844 (5.6%)
9.5 – 12.0 mg/dL	6,510 (63.1%)	9,198 (58.4%)	6,914 (62.8%)	8,794 (58.4%)
> 12.0 mg/dL	3,214 (31.1%)	5,641 (35.8%)	3,437 (31.2%)	5,418 (36.0%)
Equilibrated Kt/V < 1.2	2,218 (21.5%)	3435 (21.8%)	2,390 (21.7%)	

Number of medications in last 30 days of baseline	5.9 ± 3.9	5.0 ± 3.7	6.0 ± 3.9	5.0 ± 3.7
Alpha blocker	101 (1.0%)	125 (0.8%)	108 (1.0%)	118 (0.8%)
ACE inhibitor	2,847 (27.6%)	3,371 (21.4%)	3,002 (27.3%)	3,216 (21.4%)
Angiotensin receptor blocker	1,451 (14.1%)	1,589 (10.1%)	1,514 (13.7%)	1,526 (10.1%)
Calcium channel blocker	4,131 (40.0%)	4,979 (31.6%)	4,348 (39.5%)	4,762 (31.6%)
Central alpha agonist	1,762 (17.1%)	2,279 (14.5%)	1,874 (17.0%)	2,167 (14.4%)
Diuretic	1,324 (12.8%)	1,469 (9.3%)	1,399 (12.7%)	1,394 (9.3%)
Vasodilator	1,344 (13.0%)	1,599 (10.2%)	1,414 (12.8%)	1,529 (10.2%)
Statin	3,079 (29.8%)	3,394 (21.6%)	3,257 (29.6%)	3,216 (21.4%)
Other cholesterol medication[c]	485 (4.7%)	547 (3.5%)	518 (4.7%)	514 (3.4%)
Digoxin	200 (1.9%)	285 (1.8%)	224 (2.0%)	261 (1.7%)
Long-acting nitrate	808 (7.8%)	959 (6.1%)	871 (7.9%)	896 (6.0%)
Antiplatelet medication	1,315 (12.7%)	1,652 (10.5%)	1,413 (12.8%)	1,554 (10.3%)
Anticoagulant medication	784 (7.6%)	1,087 (6.9%)	856 (7.8%)	1,015 (6.7%)
Midodrine	159 (1.5%)	239 (1.5%)	175 (1.6%)	223 (1.5%)

All-covariates were measured during the baseline period prior to beta block initiation. Values are given as number (%) for categorical variables and as mean ± standard deviation for continuous variables.

[a] Claims-based definition of non-compliance included ICD-9 discharge diagnosis codes V15.81 (personal history of noncompliance with medical treatment, presenting hazards to health) and V45.12 (noncompliance with renal dialysis).

[b] Patients were considered as having a recent history of intradialytic hypotension if they had an intradialytic nadir systolic blood pressure < 90 mmHg in at least 30% of outpatient hemodialysis treatments in the last 30 days of the baseline period.[57]

[c] Other cholesterol medications included the following non-statin cholesterol medications: bile acid sequestrants, cholesterol absorption inhibitors, fibrates and niacin.

Abbreviations: ACE, angiotensin converting enzyme; BP, blood pressure; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; GI, gastrointestinal; ICD-9, International Classification of Diseases, Ninth Revision.

Table 5.2 Association between beta blocker adherence versus non-adherence and 1-year mortality

Adherence metric	n	No. events (%)	Rate per 1,000 p-y	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Standard PDC					
PDC < 80% (non-adherent)	15,747	2,449 (15.6%)	19.6	1.00 (ref.)	1.00 (ref.)
PDC ≥ 80% (adherent)	10,324	1,406 (13.6%)	17.3	0.88 (0.83, 0.94)	0.84 (0.79, 0.90)
Modified PDC					
PDC < 80% (non-adherent)	15, 056	2,234 (14.8%)	18.6	1.00 (ref.)	1.00 (ref.)
PDC ≥ 80% (adherent)	11,015	1,621 (14.7%)	18.7	1.01 (0.94, 1.08)	0.91 (0.85, 0.97)

A total of 26,071 hemodialysis patients were included in the full study cohort. Multivariable Cox proportional hazards models, adjusting for baseline covariates specified in Table 5.1, were used to estimate the associations beta blocker adherence versus non-adherence blocker adherence and 1-year all-cause mortality.

Abbreviations: CI, confidence interval; HR, hazard ratio; no., number; p-y, person-years; ref., referent

Table 5.3 Association between beta blocker adherence versus non-adherence and 1-year mortality among individuals who filled an index beta blocker with a days supply of ≤ 30 days

Adherence metric	n	No. events (%)	Rate per 1,000 p-y	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Standard PDC					
PDC < 80% (non-adherent)	13,490	2,111 (15.7%)	19.6	1.00 (ref.)	1.00 (ref.)
PDC ≥ 80% (adherent)	8.004	1,170 (13.8%)	18.4	0.89 (0.82, 0.95)	0.83 (0.78, 0.90)
Modified PDC					
PDC < 80% (non-adherent)	12,878	1,917 (14.9%)	18.6	1.00 (ref.)	1.00 (ref.)
PDC ≥ 80% (adherent)	8,616	1,301 (15.1%)	19.1	1.03 (0.96, 1.10)	0.91 (0.85, 0.98)

A total of 21,949 hemodialysis patients filled an index beta blocker with a days supply ≤ 30 days. Multivariable Cox proportional hazards models, adjusting for baseline covariates specified in Table 5.1, were used to estimate the associations beta blocker adherence versus non-adherence blocker adherence and 1-year all-cause mortality.

Abbreviations: CI, confidence interval; HR, hazard ratio; no., number; p-y, person-years; ref., referent

Table 5.4 Association between beta blocker adherence versus non-adherence and 1-year mortality among patients with the low-income subsidy benefit

Adherence metric	n	No. events (%)	Rate per 1,000 p-y	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Standard PDC					
PDC < 80% (non-adherent)	12,275	1,792 (14.6%)	18.1	1.00 (ref.)	1.00 (ref.)
PDC ≥ 80% (adherent)	8,186	1,037 (12.7%)	15.9	0.88 (0.81, 0.95)	0.84 (0.78, 0.91)
Modified PDC					
PDC < 80% (non-adherent)	11,692	1,611 (13.8%)	17.0	1.00 (ref.)	1.00 (ref.)
PDC ≥ 80% (adherent)	8,769	1,218 (13.9%)	17.6	1.03 (0.96, 1.11)	0.93 (0.86, 1.00)

A total of 20,461 hemodialysis patients had the low-income subsidy benefit. Multivariable Cox proportional hazards models, adjusting for baseline covariates specified in Table 5.1, were used to estimate the associations beta blocker adherence versus non-adherence blocker adherence and 1-year all-cause mortality.

Abbreviations: CI, confidence interval; HR, hazard ratio; no., number; p-y, person-years; ref., referent

Figures

Figure 5.1 Aim 2 Study design

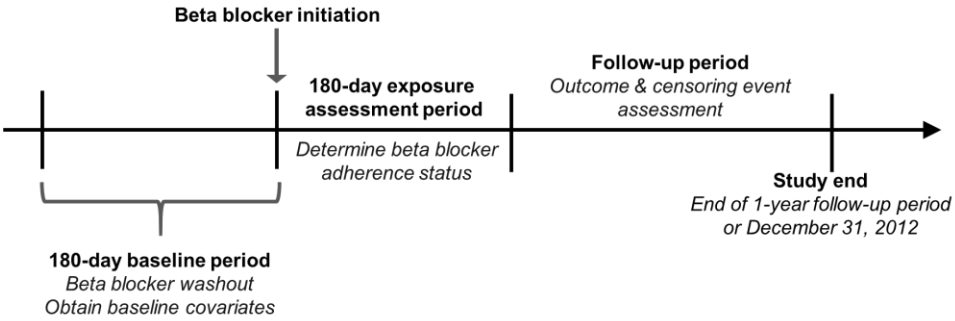
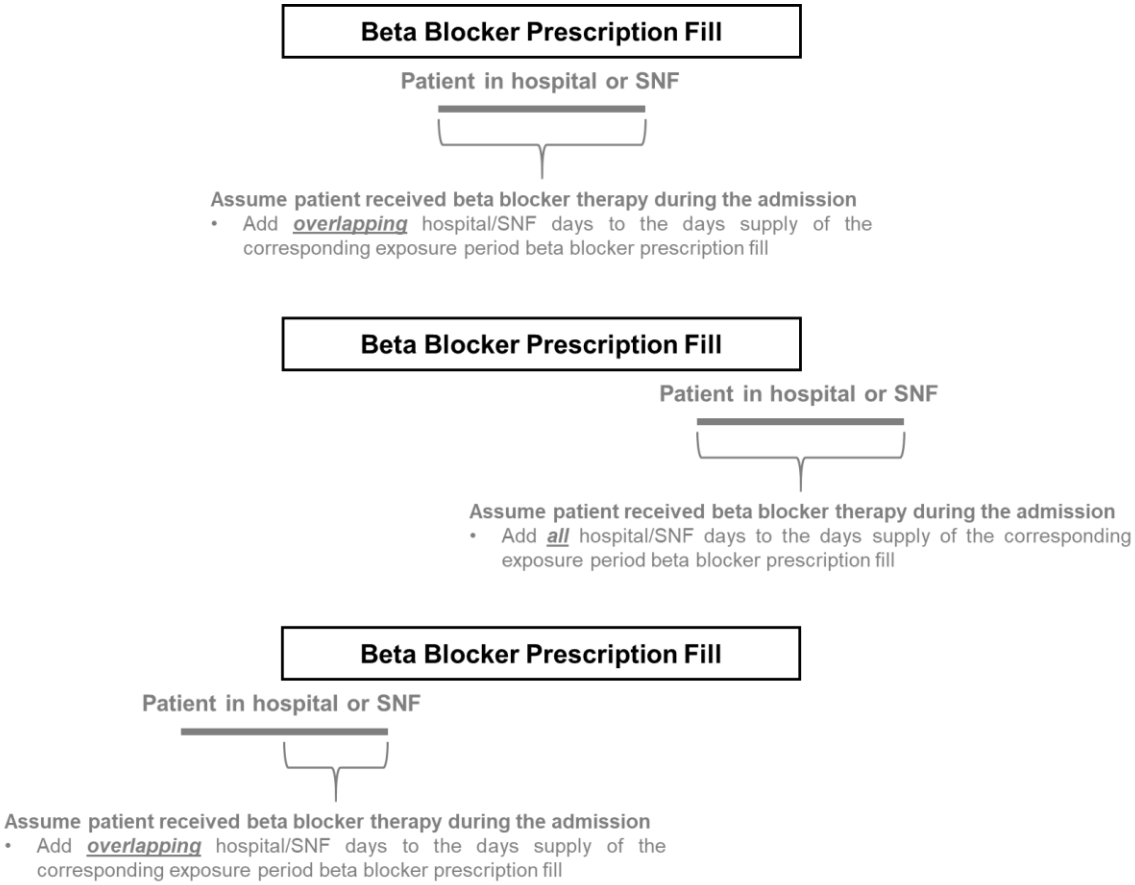
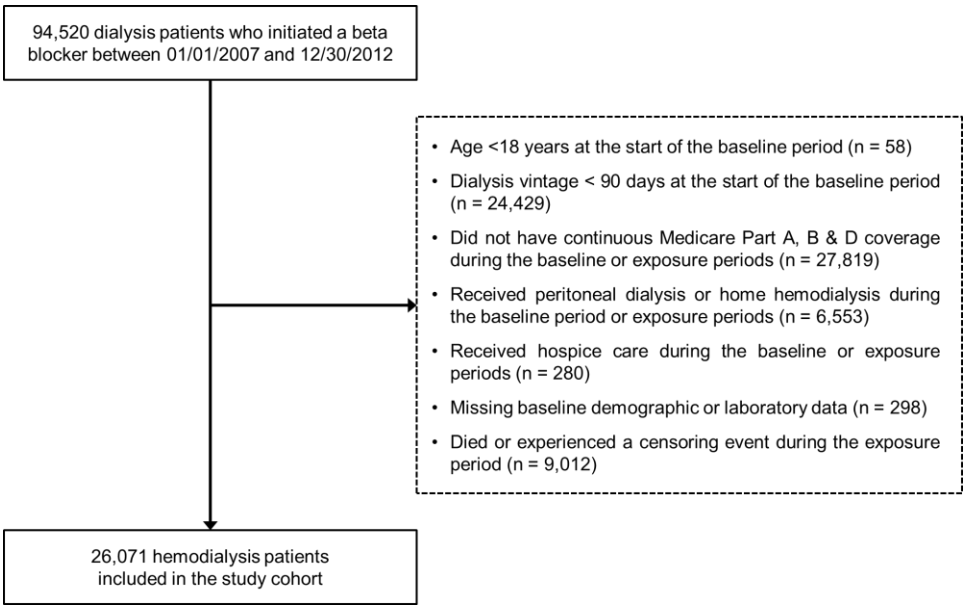


Figure 5.2 Illustration of beta blocker days supply adjustment made when patients were admitted to the hospital or skilled nursing facility in Aim 2 analyses



Abbreviations: SNF, skilled nursing facility.

Figure 5.3 Aim 2 study flow diagram



CHAPTER 6: RESULTS AIM 3

Introduction

Individuals receiving maintenance hemodialysis have cardiovascular mortality rates that exceed those of the general population by 5 to 7-fold.[1] Cardioprotective medications such as beta blockers, among others, are often prescribed to reduce cardiovascular risk. However, clinical trials establishing the cardioprotective nature and safety of beta blockers largely excluded individuals with ESRD.[2, 3]Approximately 65% of the U.S. hemodialysis population is treated with a beta blocker.[5] Despite widespread use, surprisingly little is known about the relative safety and efficacy of different beta blockers in hemodialysis patients, a population with special drug dosing considerations.

Within the beta blocker class, individual medications possess different pharmacologic and pharmacokinetic properties. Pharmacologically, beta blockers differ with respect to their beta-adrenergic receptor selectivity and vasodilatory capabilities. Kinetically, physiochemical factors, such as molecular size, hydrophilicity, plasma-protein binding, and volume of distribution influence the extent of beta blocker clearance by the hemodialysis procedure (i.e. dialyzablity). These key differences may plausibly alter the hemodynamic and antiarrhythmic risk-benefit profiles of individual beta blockers in the setting of ESRD.

In fact, observational data suggests that the potential survival benefit conferred by beta blockers may differ across agents. In a Canadian cohort, Weir *et al.* found that the risk of all-cause death was significantly higher among hemodialysis patients treated with high dialyzablity beta blockers (acebutolol, atenolol, metoprolol tartrate) as compared to patients treated with low

dialyzablity beta blockers (bisoprolol and propranolol).[46] However, carvedilol and metoprolol succinate, two commonly prescribed beta blockers in the U.S.,[5] were not considered due to provincial prescription formulary restrictions. Carvedilol is a non-selective beta blocker with additional alpha-blocking effects and is minimally cleared by hemodialysis. Metoprolol (tartrate and succinate) is a cardioselective beta blocker and is extensively cleared by hemodialysis. The marked pharmacologic and pharmacokinetic heterogeneity between carvedilol and metoprolol may differentially influence clinical outcomes and safety among individuals receiving maintenance hemodialysis and warrants further study.

While a head-to-head randomized clinical trial would be the ideal approach to investigating the comparative safety and efficacy of carvedilol and metoprolol in the dialysis population, a recent feasibility study suggested that recruitment for such a trial may be challenging.[45] Well-designed pharmacoepidemiologic studies are thus needed to inform clinical decision-making. We undertook this study to investigate the association between carvedilol versus metoprolol initiation and 1-year mortality in a cohort of prevalent, maintenance in-center hemodialysis patients treated by a large U.S. dialysis organization.

Methods

Data source

The study data were extracted from the clinical database of a large U. S. dialysis organization and the USRDS. Data were linked at the patient level. The dialysis organization operates over 1,500 outpatient dialysis clinics throughout the nation. Its database captures detailed demographic, clinical, laboratory, and dialysis treatment data. Laboratory data are measured on a biweekly or monthly basis. Hemodialysis treatment parameters are recorded on a treatment-to-

treatment basis. The USRDS is a national ESRD surveillance system that includes: the Medical Evidence and ESRD Death Notification forms, the Medicare Enrollment database (a repository of Medicare beneficiary enrollment and entitlement data), and Medicare standard analytic files (final action administrative claims data including Medicare Parts A, B and D).

Study design and population

We conducted a retrospective cohort study using a new-user design[77] to investigate the association between carvedilol versus metoprolol initiation and 1-year all-cause and cardiovascular mortality (separately) among individuals receiving maintenance hemodialysis. **Figure 6.1** displays the study design. First, using Medicare Part D claims, we identified dialysis patients treated at the large dialysis organization who initiated oral beta blocker therapy from January 1, 2007 to December 30, 2012 following a 180-day washout period free of any documented oral beta blocker use. We then applied the following exclusion criteria: 1) age < 18 years old at the start of the baseline period, 2) dialysis vintage ≤ 90 days at the start of the baseline period, 3) lack of continuous Medicare Part A, B and D coverage during the baseline period, 4) receipt of home hemodialysis or peritoneal dialysis during the baseline period, 5) receipt of < 6 center-based hemodialysis treatments in the last 30 days of the baseline period, 6) receipt of hospice care during the baseline period, 7) missing demographic or laboratory data, and 8) initiation of a beta blocker other than carvedilol or metoprolol. Thus, the study cohort consisted of prevalent, adult hemodialysis patients who were carvedilol or metoprolol new-users.

Exposure, outcomes, and censoring events

The exposures of interest were carvedilol and metoprolol initiation. The index date was designated as the date of the first carvedilol or metoprolol prescription after the washout period. Study outcomes of interest were 1-year all-cause and cardiovascular mortality (assessed

separately). Cardiovascular mortality was defined using the USRDS definition (**Table 6.1**).[84] Individuals were followed forward in historical time from the index date to the first occurrence of a study outcome or censoring event. Censoring events included: kidney transplantation, dialysis modality change, recovery of renal function, loss of Medicare Part A, B or D coverage, being lost to follow-up, reaching 1-year of follow-up post-index date, or study end (December 31, 2012).

Baseline covariate determination

Baseline covariates included potential confounders and variables known to be strong risk factors for death in the hemodialysis population.[85] Covariates were identified in the 180 days prior to the index date and included: patient demographics, comorbid conditions, laboratory data, dialysis treatment parameters, and prescription medication use (**Appendix: Supplemental Table 1**).

Statistical analysis

Baseline characteristics are described across carvedilol and metoprolol initiators as count (%) for categorical variables and mean ± standard deviation for continuous variables. Baseline covariate distributions were compared using standardized differences. A standardized difference >0.1 represents meaningful imbalance between treatment groups.[80]

In primary analyses, we used an intent-to-treat approach to evaluate the association between carvedilol (versus metoprolol) initiation and 1-year all-cause and cardiovascular mortality. Cox proportional hazards models were used to assess the study medication—all-cause mortality association. Fine and Gray proportional subdistribution hazards models[81] that treated non-cardiovascular death as a competing risk were used to assess the study medication—cardiovascular mortality association. Both models estimate HRs and their 95% CIs. IPT weighting was used to control for confounding. We used multivariable logistic regression to calculate the

predicted probability (i.e. propensity score) of receiving carvedilol (versus metoprolol) as a function of baseline covariates. Propensity scores were used to generate IPT weights.[82] We estimated adjusted HRs by applying IPT weights in regression models.

In secondary analyses, using methods analogous to primary analyses, we assessed the association between carvedilol (versus metoprolol) initiation and 1-year morality in clinically relevant subgroups including individuals with hypertension, atrial fibrillation, heart failure and myocardial infraction, the main cardiovascular indications for beta blocker therapy.

We conducted several sensitivity analyses to assess the robustness of our primary results. First, since the effect of metoprolol (versus carvedilol) on all-cause mortality may differ by metoprolol formulation,[86] we repeated primary analyses and separately compared: 1) carvedilol versus metoprolol tartrate (the immediate release formulation), and 2) carvedilol versus metoprolol succinate (the controlled/extended release formulation). Second, since beta blocker therapy is typically titrated, we repeated primary analyses restricted the cohort to patients who initiated on low doses carvedilol (≤ 25 mg) or metoprolol (≤ 100 mg). Third, since Medicare Part D beneficiaries who have supplemental low-income subsidy coverage receive prescription medications at very little or no cost, these individuals are less likely to obtain medications without using their prescription insurance benefit. We thus repeated, primary analyses in the subset of study patients with the low-income subsidy benefit. Fourth, we repeated primary analyses using an on-treatment (i.e. per-protocol) approach. In these analyses, index beta blocker discontinuation and switching to a non-index beta blocker during follow-up were considered additional censoring events. A discontinuation event occurred when the days supply of the index beta blocker medication was exhausted for > 60 days (a grace/gap period to allow for imperfect adherence) without a subsequent dispensing. The end of the 60-day grace period was considered the

discontinuation date. was Beta blocker medication days supply were adjusted for hospital and skilled nursing facility admissions. Fifth, we tested the specificity of our findings by examining the association between carvedilol (versus metoprolol) initiation and hospitalized bowel obstruction, a tracer (i.e. negative control) outcome that we did not expect to be influenced by the utilization of either of the study medications.

Finally, we conducted additional *post hoc* analyses to evaluate potential mechanistic explanations for our study findings. We assessed the association between carvedilol (versus metoprolol) initiation and the occurrence of intradialytic hypotension by estimating incidence rate ratios (IRRs) and their 95% CIs using Poisson regression. Episodes of intradialytic hypotension were identified using two different definitions: 1) a systolic blood pressure decline ≥ 20 mmHg during dialysis accompanied by saline administration (a guideline-based definition);[87-89] and 2) an intradialytic nadir systolic blood pressure < 90 mmHg (a definition shown to associate with mortality).[57]

Results

Study cohort characteristics

Figure 6.2 displays a flow diagram of study cohort selection. A total of 27,064 individuals receiving maintenance hemodialysis were included in the study: 9,558 (35.3%) carvedilol initiators and 17,506 (64.7%) metoprolol initiators. Overall, study patients had an average age of 59.6 ± 14.7 years, 46.7% were female, 42.9% were black, 19.5% were Hispanic and the most common ESRD cause was diabetes (49.0%). Cardiovascular comorbidities were common; 13.9% of the cohort had atrial fibrillation, 29.9% had coronary atherosclerosis, 72.7% had hypertension, 34.6% had heart failure, 6.6% had a recent myocardial infarction, and 21.7% had peripheral arterial disease.

The propensity score distribution of carvedilol and metoprolol initiators exhibited substantial overlap (**Figure 6.3**), indicating that the study groups were highly comparable. Patient baseline characteristics stratified by study beta blocker are presented in **Table 6.2**. Before IPT weighting, baseline covariates were generally well-balanced between treatment groups (standardized differences ≤ 0.1), with a few exceptions (year of index carvedilol or metoprolol initiation, heart failure and an ESRD cause of diabetes). After IPT weighting all baseline covariates were well-balanced between treatment groups.

Primary analyses

Under the intent-to-treat paradigm, the study cohort was followed for a total of 20,863 person-years (7,219 person-years for carvedilol initiators and 13,644 metoprolol initiators). The average duration of follow-up was 275 days for carvedilol initiators and 285 days for metoprolol initiators. During follow-up 4,296 all-cause deaths (1,625 in the carvedilol group and 2,671 in the metoprolol group) and 1,943 cardiovascular deaths (782 in the carvedilol group and 1,161 in the metoprolol group) occurred. **Figure 6.4** displays the associations between carvedilol (versus metoprolol) initiation and 1-year all-cause and cardiovascular mortality. Compared to individuals initiating metoprolol, individuals initiating carvedilol had a higher rate of all-cause mortality (225.1 versus 195.8 events/1,000 person-years; adjusted HR [95% CI] = 1.09 [1.02, 1.16]) and cardiovascular mortality (108.3 versus 85.1 events/100 person-years; adjusted HR [95% CI] = 1.19 [1.08, 1.30]).

Secondary analyses

Secondary analyses assessing associations between carvedilol (versus metoprolol) initiation and mortality among individuals with hypertension, atrial fibrillation, heart failure or a recent myocardial infarction produced results analogous to primary study findings (**Table 6.3**).

Sensitivity analyses

Sensitivity analyses comparing carvedilol initiators to metoprolol tartrate and metoprolol succinate initiators (separately) generated results similar to primary analyses. Treatment with carvedilol (versus metoprolol) was associated increased 1-year all-cause and cardiovascular mortality, regardless of the comparator metoprolol formulation (**Table 6.4**). In addition, separate sensitivity analyses restricting the study cohort to 1) individuals who initiated a low-dose study beta blocker, and 2) patients with the Medicare Part D low-income subsidy benefit, also produced results similar results to primary analyses (**Tables 6.5 and 6.6**).

In sensitivity analyses using an on-treatment paradigm, the study cohort was followed for a total of 14,460 person-years (5,127 person-years for carvedilol-treated patients and 9,333 person-years for metoprolol-treated patients). During follow-up there were 2,941 all-cause deaths (1,117 in the carvedilol group and 1,824 in the metoprolol group) and 1,341 cardiovascular deaths (544 in the carvedilol group and 797 in the metoprolol group) occurred. A total of 11,110 individuals discontinued index beta blocker therapy and 1,662 switched to a different beta blocker during follow-up. The average duration of continuous index medication use was 195 days for both carvedilol initiators metoprolol initiators. Individuals who remained on carvedilol (versus metoprolol) treatment trended toward higher rates of all-cause mortality (217.9 versus 195.4 events/1,000 person-years; adjusted HR [95% CI] = 1.06 [0.98, 1.14]) and had higher rates cardiovascular mortality (106.1 versus 85.4 events/1,000 person-years; adjusted HR [95% CI] = 1.15 [1.03, 1.29]).

In sensitivity analyses evaluating the study medication—tracer outcome association, carvedilol (versus metoprolol) initiation was not associated with the occurrence of hospitalized

bowel obstruction (rate of 30.3 versus 28.7 events/1,000 person-years; adjusted HR [95% CI] = 1.02 [0.86, 1.20]).

Post hoc analyses

The rate of intradialytic hypotension (systolic BP decline ≥ 20 mmHg during hemodialysis accompanied by saline administration) during study follow-up was higher among carvedilol (versus metoprolol) initiators (57.5 versus 55.2 episodes/1,000 person-treatments; adjusted IRR [95% CI] = 1.10 [1.09, 1.11]). Similar findings were observed when an episode of intradialytic hypotension was defined as an intradialytic nadir systolic blood pressure < 90 mmHg (comparing carvedilol to metoprolol initiators: rate of 144.4 versus 136.5 episodes/1,000-person-treatments; adjusted IRR [95% CI] = 1.02 [1.01, 1.03] comparing carvedilol to metoprolol initiators).

Discussion

To our knowledge, this is the first published study evaluating the comparative mortality risk of carvedilol and metoprolol among individuals receiving maintenance hemodialysis. We demonstrated that carvedilol (versus metoprolol) initiation was associated with increased 1-year all-cause and cardiovascular mortality. The associations were consistent within clinically relevant subgroups and robust across sensitivity analyses. We also found that carvedilol initiators experienced significantly higher rates of intradialytic hypotension compared to metoprolol initiators.

To date, there have been no randomized clinical trials comparing the efficacy and safety of individual beta blockers in the dialysis population. Prior beta blocker clinical trials were either placebo-controlled[23, 45] or compared beta blockers to other antihypertensive classes (e.g. angiotensin-converting enzyme inhibitors).[44] Existing observational investigations have

predominantly focused on comparing beta blocker users to non-users,[16, 66, 68, 69, 72-74] and only two observational studies considered head-to-head beta blocker comparisons. Weir *et al*. assessed the association between beta blocker dialyzability and 180-day mortality in a cohort of 6,588 elderly, Canadian hemodialysis patients.[46] Initiation of a highly dialyzable beta blocker versus a minimally-dialyzable beta blocker was associated with increased all-cause death. This study provided initial evidence that beta blocker heterogeneity may differentially impact clinical outcomes in the hemodialysis population, but, carvedilol (a minimally dialyzable beta blocker) and metoprolol succinate (a highly dialyzable beta blocker) were not considered. In the U.S., carvedilol and metoprolol succinate account for 50% of all beta blocker prescriptions.

In a second epidemiologic study, Shireman *et al*. evaluated the association between beta blocker selectivity and mortality in a cohort of 4,398 incident U.S. hemodialysis and peritoneal dialysis patients with dual Medicare/Medicaid coverage and hypertension.[47] Initiation of a cardioselective beta blocker (atenolol, metoprolol) versus a non-selective beta blocker (carvedilol, labetalol) was associated with increased survival. However, the relative contributions of carvedilol and metoprolol to the observed association are unclear, and this investigation relied on data from 2000-2005. In the last decade, carvedilol use has risen,[5, 41] rendering a contemporary analysis important. In fact, international guideline bodies have called for additional comparative effectiveness research on putative cardioprotective drugs such as beta blockers in the hemodialysis population.[4]

To begin to address this evidence gap, we performed a head-to-head comparison of the two most commonly prescribed beta blockers in the U.S., carvedilol and metoprolol. We found that carvedilol (versus metoprolol) initiation was associated with higher 1-year all-cause and cardiovascular mortality. Results were consistent among individuals with hypertension, atrial

fibrillation, heart failure, and a recent myocardial infarction. Furthermore, the observed study beta blocker—mortality association was robust across sensitivity analyses comparing carvedilol to immediate-release metoprolol tartrate and extended/controlled-release metoprolol succinate (separately). In *post hoc* analyses, we found that the occurrence of intradialytic hypotension (defined two ways) was more common after carvedilol (versus metoprolol) initiation. Given that recurrent intradialytic hypotension is associated with increased morbidity and mortality in the hemodialysis population,[57, 63, 64, 90] the results from our *post hoc* analyses support the notion that hemodynamic instability may play a mechanistic role in the observed association between carvedilol (versus metoprolol) initiation and greater mortality.

Pharmacologic and kinetic differences between carvedilol and metoprolol may plausibly explain the observed difference in mortality and intradialytic hypotension occurrence. First, the extent to which a beta blocker is removed from circulation by hemodialysis may impact intradialytic blood pressure. Carvedilol is minimally dialyzable, and metoprolol is highly dialyzable. As a result, carvedilol's antihypertensive effects are likely maintained over the course of dialysis, whereas metoprolol's blood pressure lowering effects may be diminished as plasma drug concentrations fall during treatment. Second, carvedilol and metoprolol differ with respect to their beta-adrenergic receptor selectivity and vasodilatory capabilities. Carvedilol is a non-selective beta blocker (beta-1 and beta-2 adrenergic receptor antagonist) with additional alpha-blocking (alpha-1 adrenergic receptor antagonist) activity. In contrast, metoprolol is a cardioselective beta blocker with high β_1 adrenergic receptor affinity. Both medications reduce heart rate and cardiac contractility, but due to its alpha-blocking effects, carvedilol is also a vasodilator. It is plausible that carvedilol-induced alpha blockade may blunt compensatory sympathetic nervous system-mediated peripheral vasoconstriction during ultrafiltration, increasing

the risk of intradialytic hemodynamic instability. These proposed clinical mechanisms likely act in concert in carvedilol-treated patients.

Ultimately, randomized controlled clinical trials are needed to definitively determine the relative safety and efficacy of carvedilol and metoprolol in the hemodialysis population. However, in the interim, our results suggest that the potential adverse hemodynamic effects of carvedilol (versus metoprolol) require consideration when prescribing beta blockers to hemodialysis patients, particularly among individuals with a history of intradialytic hemodynamic instability. For example, it may be reasonable to: 1) consider metoprolol over carvedilol among individuals at higher risk for intradialytic hypotension; or 2) recommend that patients hold carvedilol doses prior to hemodialysis treatments to minimize potential intradialytic hypotensive effects. However, such decisions must be made carefully on an individual basis with consideration of comorbid cardiovascular conditions, historical blood pressure patterns and concomitant antihypertensive medication use and dosing.

Our study has several strengths. First, we used modern pharmacoepidemiologic study design to evaluate the comparative mortality risks associated with carvedilol and metoprolol treatment. To minimize the influence of bias due to confounding by indication or disease severity, we selected study medications with similar indications and therapeutic roles.[91] Notably, the carvedilol and metoprolol initiators were highly comparable, and all baseline covariate imbalances between treatment groups were diminished after IPT weighting. Additionally, we chose to study the two most commonly prescribed beta blockers to closely mirror a real-world clinical practice decision.[91] Second, unlike previous claims-based studies, we utilized a linked data set with detailed clinical data that enabled us to account for many important biochemical indices and dialysis

treatment parameters in our analyses. Finally, we performed multiple sensitivity analyses to test the robustness of our findings.

Our results should be considered in the context of study limitations First, our study was observational, and it is possible that residual confounding may exist. To minimize confounding from difficult-to-measure factors such as ambient health status, we controlled for variables including albumin, phosphorus, and a history of non-compliance. Reassuringly, carvedilol (versus metoprolol) initiation was not associated with the occurrence of the tracer outcome, hospitalized bowel obstruction. Second, while our linked data source was comprised of detailed administrative and clinical data, information on some potentially important factors, such as the timing of medication dosing, were not available. Third, comorbid condition designations were based upon ICD-9 diagnosis codes. Comorbidities not requiring a healthcare encounter during the 180-day baseline period may have been missed. Fourth, our study population was comprised of individuals receiving center-based maintenance hemodialysis who initiated carvedilol or metoprolol. Our results should not be extrapolated to excluded populations such as home hemodialysis or peritoneal dialysis patients, or hemodialysis patients receiving other beta blockers. Finally, our study evaluated a cohort of U.S. hemodialysis patients. Our results may not apply to other countries where national or regional prescription formularies limit metoprolol and/or carvedilol prescribing.

In conclusion, we observed that carvedilol (versus metoprolol) initiation was associated with higher 1-year all-cause and cardiovascular mortality in a cohort of U.S. hemodialysis patients. Data from our *post hoc* analyses suggest that one potential mechanism for the observed mortality associations may be an increased rate of intradialytic hypotension after carvedilol (versus metoprolol) initiation. Given the unique pharmacokinetic and hemodynamic considerations in the

ESRD population, additional study of the efficacy and safety of beta blockers, as well as other cardioprotective medications with antihypertensive properties is needed.

Tables

Table 6.1 Aim 3 Outcome definitions

Main study outcomes		
Clinical outcome	**Data source**	**Specification**
All-cause mortality	USRDS Patients File	Death due to any cause
Cardiovascular mortality[84]	USRDS Patients File	Death with any cardiovascular death code (23, 25, 26, 27, 28, 29, 30, 31, 32, 35 or 36) listed as the primary cause of death on the ESRD death notification form[a]
Tracer outcome		
Clinical outcome	**Data source**	**Specification**
Hospitalized bowel obstruction	USRDS Medicare Part A Claims	Claim for an inpatient hospital admission with a bowel obstruction ICD-9 discharge diagnosis code (560) located in the any billing position[b]

[a] The cardiovascular cause of death codes include the following clinical conditions: acute myocardial infarction, pericarditis (including cardiac tamponade), atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest (cause unknown), valvular heart disease, pulmonary edema due to exogenous fluid, congestive heart failure, pulmonary embolus and cerebrovascular accident (including intracranial hemorrhage).

[b] Specified three-digit ICD-9 diagnosis code categories included all existing 4th and 5th digit diagnosis codes.

Abbreviations: ESRD, end-stage renal disease; ICD-9, International Classification of Diseases, 9th Revision; USRDS, United States Renal Data System.

Table 6.2 Baseline characteristics of study patients initiating carvedilol and metoprolol

Characteristic	Unweighted			Weighted		
	Carvedilol n = 9,558	Metoprolol n = 17,506	Standardized difference[a]	Carvedilol n = 9,532	Metoprolol n = 17,522	Standardized difference[a]
Age (years)	59.8 ±14.4	59.5 ±14.9	0.026	59.8 ± 14.4	59.5 ± 14.9	0.026
Female	4,314 (45.1%)	8,316 (47.5%)	0.048	4,444 (46.6%)	8,184 (46.7%)	0.002
Race						
White	4,848 (50.7%)	9,054 (51.7%)	0.020	4,880 (51.2%)	8,992 (51.3%)	0.002
Black	4,186 (43.8%)	7,419 (42.4%)	0.029	4,102 (43.0%)	7,525 (42.9%)	0.002
Other	524 (5.5%)	1,033 (5.9%)	0.018	549 (5.8%)	1,006 (5.7%)	0.001
Hispanic ethnicity	1,925 (20.1%)	3,351 (19.1%)	0.025	1,867 (19.6%)	3,420 (19.5%)	0.002
Low-income subsidy	7,259 (75.9%)	13,524 (77.3%)	0.031	7,326 (76.9%)	13,463 (76.8%)	0.001
Year index beta blocker was prescribed						
2007	1,339 (14.0%)	3,364 (19.2%)	0.140	1,632 (17.1%)	3,035 (17.3%)	0.005
2008	1,385 (14.5%)	3,011 (17.2%)	0.074	1,534 (16.1%)	2,834 (16.2%)	0.002
2009	1,440 (15.1%)	2,561 (14.6%)	0.012	1,405 (14.7%)	2,588 (14.8%)	0.001
2010	1,524 (15.9%)	2,696 (15.4%)	0.015	1,495 (15.7%)	2,734 (15.6%)	0.002
2011	1,804 (18.9%)	2,852 (16.3%)	0.068	1,664 (17.5%)	3,029 (17.3%)	0.005
2012	2,066 (21.6%)	3,022 (17.3%)	0.110	1,801 (18.9%)	3,303 (18.9%)	0.001
Cause of ESRD						
Diabetes	5,027 (52.6%)	8,227 (47.0%)	0.112	4,703 (49.3%)	8,607 (49.1%)	0.004
Hypertension	2,563 (26.8%)	5,051 (28.9%)	0.045	2,684 (28.2%)	4,927 (28.1%)	0.001
Glomerular disease	909 (9.5%)	1,936 (11.1%)	0.051	982 (10.3%)	1,829 (10.4%)	0.004
Other	1,059 (11.1%)	2,292 (13.1%)	0.062	1,162 (12.2%)	2,160 (12.3%)	0.004
Body mass index						
< 18.5 kg/m^2	474 (5.0%)	844 (4.8%)	0.006	464 (4.9%)	854 (4.9%)	0.000
18.5 – 24.9 kg/m^2	3,555 (37.2%)	6,285 (35.9%)	0.027	3,474 (36.4%)	6,371 (36.4%)	0.002
25.0 – 29.9 kg/m^2	2,761 (28.9%)	4,978 (28.4%)	0.010	2,718 (28.5%)	5,005 (28.6%)	0.001
≥ 30.0 kg/m^2	2,768 (29.0%)	5,399 (30.8%)	0.041	2,875 (30.2%)	5,292 (30.2%)	0.001

History of prior renal transplant	502 (5.3%)	1,204 (6.9%)	0.068	594 (6.2%)	1,103 (6.3%)	0.003
Dialysis vintage						
< 1.0 year	595 (6.2%)	935 (5.3%)	0.038	535 (5.6%)	987 (5.6%)	0.001
1.0 – 1.9 years	2,118 (22.2%)	3,705 (21.2%)	0.024	2,052 (21.5%)	3,778 (21.6%)	0.001
2.0 – 2.9 years	1,668 (17.5%)	2,778 (15.9%)	0.042	1,556 (16.3%)	2,875 (16.4%)	0.002
≥ 3.0 years	5,177 (54.2%)	10,088 (57.6%)	0.070	5,388 (56.5%)	9,882 (56.4%)	0.003
Atrial fibrillation	1,236 (12.9%)	2,525 (14.4%)	0.043	1,298 (13.6%)	2,425 (13.8%)	0.006
Other arrhythmia	930 (9.7%)	1,630 (9.3%)	0.014	906 (9.5%)	1,657 (9.5%)	0.002
Angina	210 (2.2%)	302 (1.7%)	0.034	180 (1.9%)	331 (1.9%)	0.000
Cancer	312 (3.3%)	661 (3.8%)	0.028	182 (1.9%)	334 (1.9%)	0.000
Conduction disorder	367 (3.8%)	496 (2.8%)	0.056	334 (3.5%)	626 (3.6%)	0.004
COPD/asthma	1,704 (17.8%)	2,795 (16.0%)	0.050	304 (3.2%)	559 (3.2%)	0.000
Coronary atherosclerosis	3,126 (32.7%)	4,960 (28.3%)	0.095	1,601 (16.8%)	2,923 (16.7%)	0.003
Diabetes	5,473 (57.3%)	9,286 (53.0%)	0.085	2,867 (30.1%)	5,252 (30.0%)	0.002
GI bleed	471 (4.9%)	932 (5.3%)	0.018	5,237 (54.9%)	9,587 (54.7%)	0.005
Heart failure	4,107 (43.0%)	5,251 (30.0%)	0.272	503 (5.3%)	911 (5.2%)	0.004
Hypertension	7,021 (73.5%)	12,652 (72.3%)	0.027	3,334 (35.0%)	6,089 (34.8%)	0.005
Liver disease	421 (4.4%)	783 (4.5%)	0.003	434 (4.6%)	784 (4.5%)	0.004
Myocardial infarction	642 (6.7%)	1,151 (6.6%)	0.006	644 (6.8%)	1,171 (6.7%)	0.003
Peripheral artery disease	2,149 (22.5%)	3,729 (21.3%)	0.029	2,096 (22.0%)	3,820 (21.8%)	0.004
Stroke	975 (10.2%)	1,876 (10.7%)	0.017	1,030 (10.8%)	1,861 (10.6%)	0.006
Valvular disease	904 (9.5%)	1,337 (7.6%)	0.065	795 (8.3%)	1,457 (8.3%)	0.001
History of non-compliance[b]	594 (6.2%)	1,021 (5.8%)	0.016	580 (6.1%)	1,051 (6.0%)	0.004
Vascular access						
Fistula	5,645 (59.1%)	10,054 (57.4%)	0.033	5,514 (57.8%)	10,150 (57.9%)	0.002
Graft	2,428 (25.4%)	4,451 (25.4%)	0.001	2,447 (25.7%)	4,470 (25.5%)	0.004
Catheter	1,485 (15.5%)	3,001 (17.1%)	0.043	1,571 (16.5%)	2,903 (16.6%)	0.002
Interdialytic weight gain ≥ 3 kg	2,377 (24.9%)	4,196 (24.0%)	0.021	2,311 (24.2%)	4,253 (24.3%)	0.001

Delivered dialysis treatment time < 240 min	7,657 (80.1%)	13,940 (79.6%)	0.012	7,626 (80.0%)	13,990 (79.8%)	0.004
Pre-dialysis systolic BP						
< 130 mmHg	1,384 (14.5%)	2,159 (12.3%)	0.063	1,241 (13.0%)	2,290 (13.1%)	0.001
130 – 149 mmHg	2,696 (28.2%)	4,744 (27.1%)	0.025	2,620 (27.5%)	4,809 (27.4%)	0.001
150 – 169 mmHg	3,175 (33.2%)	6,084 (34.8%)	0.032	3,251 (34.1%)	5,996 (34.2%)	0.002
≥170 mmHg	2,303 (24.1%)	4,519 (25.8%)	0.040	2,419 (25.4%)	4,428 (25.3%)	0.003
Recent history of intradialytic hypotension[c]	1,349 (14.1%)	2,363 (13.5%)	0.018	1,322 (13.9%)	2,415 (13.8%)	0.002
Albumin						
≤ 3.0 g/dL	468 (4.9%)	883 (5.0%)	0.007	483 (5.1%)	877 (5.0%)	0.003
3.1 – 4.0 g/dL	6,221 (65.1%)	11,057 (63.2%)	0.040	6,091 (63.9%)	11,192 (63.9%)	0.001
> 4.0 g/dL	2,869 (30.0%)	5,566 (31.8%)	0.038	2,958 (31.0%)	5,453 (31.1%)	0.002
Calcium						
< 8.5 mg/dL	1,338 (14.0%)	2,497 (14.3%)	0.008	1,352 (14.2%)	2,488 (14.2%)	0.000
8.5 – 10.2 mg/dL	7,756 (81.1%)	14,159 (80.9%)	0.007	7,712 (80.9%)	14,181 (80.9%)	0.000
> 10.2 mg/dL	464 (4.9%)	850 (4.9%)	0.000	467 (4.9%)	853 (4.9%)	0.001
Phosphorus						
< 3.5 mg/dL	1,088 (11.4%)	1,907 (10.9%)	0.016	1,050 (11.0%)	1,936 (11.0%)	0.001
3.5 – 5.5 mg/dL	5,224 (54.7%)	9,431 (53.9%)	0.016	5,175 (54.3%)	9,497 (54.2%)	0.002
> 5.5 mg/dL	3,246 (34.0%)	6,168 (35.2%)	0.027	3,307 (34.7%)	6,090 (34.8%)	0.001
Potassium						
< 4.0 mEq/L	1,064 (11.1%)	1,918 (11.0%)	0.006	1,047 (11.0%)	1,931 (11.0%)	0.001
4.0 – 6.0 mEq/L	8,152 (85.3%)	14,915 (85.2%)	0.003	8,124 (85.2%)	14,935 (85.2%)	0.000
> 6.0 mEq/L	342 (3.6%)	673 (3.8%)	0.014	360 (3.8%)	656 (3.7%)	0.002
Hemoglobin						
< 9.5 g/dL	663 (6.9%)	1,166 (6.7%)	0.011	651 (6.8%)	1,186 (6.8%)	0.003
9.5 – 12.0 mg/dL	6,164 (64.5%)	10,709 (61.2%)	0.069	5,970 (62.6%)	10,943 (62.4%)	0.004
> 12.0 mg/dL	2,731 (28.6%)	5,631 (32.2%)	0.078	2,911 (30.5%)	5,394 (30.8%)	0.005
Equilibrated Kt/V < 1.2	2,235 (23.4%)	3,850 (22.0%)	0.033	2,145 (22.5%)	3,943 (22.5%)	0.000
Number of medications in last 30 days of baseline	5.5 ± 3.8	5.5 ± 3.9	0.014	5.5 ± 3.9	5.5 ± 3.9	0.014
Alpha blocker	63 (0.7%)	168 (1.0%)	0.034	83 (0.9%)	151 (0.9%)	0.002

ACE inhibitor	2,232 (23.4%)	4,040 (23.1%)	0.006	2,223 (23.3%)	4,070 (23.2%)	0.002
Angiotensin receptor blocker	1,212 (12.7%)	1,848 (10.6%)	0.066	1,102 (11.6%)	2,003 (11.4%)	0.004
Calcium channel blocker	3,060 (32.0%)	5,959 (34.0%)	0.043	3,193 (33.5%)	5,853 (33.4%)	0.002
Central alpha agonist	1,272 (13.3%)	2,486 (14.2%)	0.026	1,338 (14.0%)	2,446 (14.0%)	0.002
Diuretic	1,239 (13.0%)	1,845 (10.5%)	0.075	1,095 (11.5%)	2,010 (11.5%)	0.001
Vasodilator	997 (10.4%)	1,916 (10.9%)	0.017	1,030 (10.8%)	1,894 (10.8%)	0.000
Statin	2,578 (27.0%)	4,509 (25.8%)	0.028	2,513 (26.4%)	4,607 (26.3%)	0.002
Other cholesterol medication[d]	394 (4.1%)	717 (4.1%)	0.001	393 (4.1%)	720 (4.1%)	0.001
Digoxin	258 (2.7%)	332 (1.9%)	0.054	206 (2.2%)	382 (2.2%)	0.002
Long-acting nitrate	845 (8.8%)	1,216 (6.9%)	0.070	733 (7.7%)	1,345 (7.7%)	0.000
Antiplatelet medication	1,280 (13.4%)	2,065 (11.8%)	0.048	1,202 (12.6%)	2,188 (12.5%)	0.004
Anticoagulant medication	711 (7.4%)	1,458 (8.3%)	0.033	754 (7.9%)	1,401 (8.0%)	0.003
Midodrine	192 (2.0%)	350 (2.0%)	0.001	192 (2.0%)	352 (2.0%)	0.000
Use of ≥ 1 potent inhibitor of CYP2D6[e]	2,690 (29.5%)	5,162 (28.1%)	0.030	2,766 (29.0%)	5,090 (29.0%)	0.001

All-covariates were measured during the baseline period prior to carvedilol or metoprolol initiation. Values for categorical variables are given as number (%) and as mean ± standard deviation for continuous variables.

[a] A standardized difference > 0.1 represents meaningful imbalance between groups.[80]

[b] Claims-based definition of non-compliance included ICD-9 discharge diagnosis codes V15.81 (personal history of noncompliance with medical treatment, presenting hazards to health) and V45.12 (noncompliance with renal dialysis).

[c] Patients were considered as having a recent history of intradialytic hypotension if they had an intradialytic nadir systolic blood pressure < 90 mmHg in at least 30% of outpatient hemodialysis treatments in the last 30 days of the baseline period.[57]

[d] Other cholesterol medications included the following non-statin cholesterol medications: bile acid sequestrants, cholesterol absorption inhibitors, fibrates and niacin.

[e] Both carvedilol and metoprolol are metabolized by cytochrome P450 2D6. Concomitant use of medications that are potent inhibitors cytochrome P450 2D6 of may increase serum concentrations of both carvedilol and metoprolol, putting patients at increased risk for beta blocker—related adverse events such as hypotension. Cytochrome P450 2D6 inhibitors included: amiodarone, bupropion, chloroquine, cinacalcet, diphenhydramine, fluoxetine, haloperidol, imatinib, paroxetine, propafenone, propoxyphene, quinidine, terbinafine and thioridazine.

Abbreviations: ACE, angiotensin converting enzyme; BP, blood pressure; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; GI, gastrointestinal; ICD-9, International Classification of Diseases, 9th Revision.

Table 6.3 Association between carvedilol versus metoprolol initiation and 1-year mortality among clinically relevant subgroups: intent-to-treat analysis[a]

Patients with hypertension (n = 19,673)									
		1-year all-cause mortality[b]				1-year cardiovascular mortality[c]			
Beta blocker	n	No. events (%)	Rate per 1,000 p-y	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[d]	No. events (%)	Rate per 1,000 p-y	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[d]
Metoprolol	12,652	2,273 (18.0%)	234.7	1.00 (ref.)	1.00 (ref.)	975 (7.7%)	100.7	1.00 (ref.)	1.00 (ref.)
Carvedilol	7,021	1,401 (20.0%)	266.0	1.13 (1.06, 1.21)	1.09 (1.02, 1.17)	664 (9.5%)	126.1	1.25 (1.13, 1.38)	1.20 (1.09, 1.32)
Patients with atrial fibrillation (n = 3,761)									
		1-year all-cause mortality[b]				1-year cardiovascular mortality[c]			
Beta blocker	n	No. events (%)	Rate per 1,000 p-y	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[d]	No. events (%)	Rate per 1,000 p-y	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[d]
Metoprolol	2,525	707 (28.0%)	406.1	1.00 (ref.)	1.00 (ref.)	303 (12.0 %)	174.1	1.00 (ref.)	1.00 (ref.)
Carvedilol	1,263	378 (30.6%)	458.4	1.13 (0.99, 1.23)	1.08 (0.94, 1.23)	178 (14.4 %)	215.9	1.23 (1.02, 1.48)	1.12 (0.93, 1.35)
Patients with heart failure (n = 9,358)									
		1-year all-cause mortality[b]				1-year cardiovascular mortality[c]			
Beta blocker	n	No. events (%)	Rate per 1,000 p-y	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[d]	No. events (%)	Rate per 1,000 p-y	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[d]
Metoprolol	5,251	1,280 (24.4%)	336.7	1.00 (ref.)	1.00 (ref.)	551 (10.5%)	144.9	1.00 (ref.)	1.00 (ref.)
Carvedilol	4,107	995 (24.2%)	335.8	1.00 (0.92, 1.08)	1.03 (0.94, 1.12)	467 (11.4%)	157.6	1.09 (0.97, 1.24)	1.12 (0.99, 1.27)
Patients with a recent myocardial infarction (n = 1,793)									
		1-year all-cause mortality[b]				1-year cardiovascular mortality[c]			
Beta blocker	n	No. events (%)	Rate per 1,000 p-y	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[d]	No. events (%)	Rate per 1,000 p-y	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[d]
Metoprolol	1,151	315 (27.4%)	395.6	1.00 (ref.)	1.00 (ref.)	149 (12.9%)	187.1	1.00 (ref.)	1.00 (ref.)
Carvedilol	642	194 (30.2%)	443.6	1.12 (0.94, 1.43)	1.04 (0.86, 1.26)	107 (16.7%)	244.7	1.31 (1.02, 1.68)	1.23 (0.96, 1.58)

An intent-to-treat design was employed in all analyses.

[a] Patient counts, event counts (% of patients) and event rates presented are based on the unweighted cohort.

[b] Cox proportional hazards models were used to estimate the associations between carvedilol (versus metoprolol) initiation and 1-year all-cause mortality.

[c] Fine and Gray proportional subdistribution hazards models were used to estimate the associations between carvedilol (versus metoprolol) initiation and 1-year cardiovascular mortality. Non-cardiovascular death was treated as a competing risk.

[d] Adjusted analyses controlled for all variables listed in Table 6.2 using inverse probability of treatment weighting. Subgroups of interest were excluded the corresponding propensity score models. For example, in subgroup analyses of patients with hypertension, the hypertension covariate was excluded from the propensity score model.

Abbreviations: CI, confidence interval; HR, hazard ratio; no., number; p-y, person-years; ref., referent

Table 6.4 Association between initiation of carvedilol versus initiation of the different metoprolol formulations and 1-year mortality: intent-to-treat analysis[a]

Carvedilol versus metoprolol tartrate (n = 21,294)									
		1-year all-cause mortality[b]				1-year cardiovascular mortality[c]			
Beta blocker	n	No. events (%)	Rate per 1,000 p-y	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[d]	No. events (%)	Rate per 1,000 p-y	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[d]
Metoprolol tartrate	11,736	1,863 (15.9%)	205.6	1.00 (ref.)	1.00 (ref.)	797 (6.8%)	87.9	1.00 (ref.)	1.00 (ref.)
Carvedilol	9,558	1,625 (17.0%)	225.1	1.09 (1.02, 1.17)	1.07 (0.99, 1.14)	782 (8.2%)	108.3	1.23 (1.11, 1.36)	1.20 (1.09, 1.32)
Carvedilol versus metoprolol succinate (n = 15,328)									
		1-year all-cause mortality[b]				1-year cardiovascular mortality[c]			
Beta blocker	n	No. events (%)	Rate per 1,000 p-y	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[d]	No. events (%)	Rate per 1,000 p-y	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[d]
Metoprolol succinate	5,770	808 (14.0%)	176.3	1.00 (ref.)	1.00 (ref.)	364 (6.3%)	79.4	1.00 (ref.)	1.00 (ref.)
Carvedilol	9,558	1,625 (17.0%)	225.1	1.27 (1.17, 1.39)	1.10 (1.00, 1.22)	782 (8.2%)	108.3	1.34 (1.19, 1.52)	1.15 (1.02, 1.30)

An intent-to-treat design was employed in all analyses.

[a] Patient counts, event counts (% of patients) and event rates presented are from the unweighted cohort.

[b] Cox proportional hazards models were used to estimate the associations between: 1) carvedilol versus metoprolol tartrate initiation and 1-year all-cause mortality; and 2) carvedilol versus metoprolol succinate initiation and 1-year all-cause mortality.

[c] Fine and Gray proportional subdistribution hazards models were used to estimate the associations between: 1) carvedilol versus metoprolol tartrate initiation and 1-year all-cause mortality; and 2) carvedilol versus metoprolol succinate initiation and 1-year all-cause mortality. Non-cardiovascular death was treated as a competing risk.

[d] Adjusted analyses controlled for all variables listed in Table 6.2 using inverse probability of treatment weighting.

Abbreviations: CI, confidence interval; HR, hazard ratio; no., number; p-y, person-years; ref., referent

Table 6.5 Association between low-dose carvedilol versus low-dose metoprolol initiation and 1-year mortality: intent-to-treat analysis[a]

Patients initiating a low-dose study beta blocker (n =22,362)									
		1-year all-cause mortality[b]				1-year cardiovascular mortality[c]			
Beta blocker	**n**	**No. events (%)**	**Rate per 1,000 p-y**	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)[d]**	**No. events (%)**	**Rate per 1,000 p-y**	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)[d]**
Metoprolol	15,028	2,441 (16.0%)	206.7	1.00 (ref.)	1.00 (ref.)	1,048 (7.0%)	89.8	1.00 (ref.)	1.00 (ref.)
Carvedilol	7,334	1,358 (18.5%)	246.8	1.19 (1.12, 1.28)	1.09 (1.02, 1.17)	6265 (9.1%)	120.9	1.33 (1.21, 1.47)	1.21 (1.10, 1.33)

An intent-to-treat design was employed in all analyses. Low dose carvedilol was defined as a total daily dose of ≤ 25 mg/day. Low dose metoprolol was defined as a total daily dose of ≤100 mg/day.

[a] Patient counts, event counts (% of patients) and event rates presented are from the unweighted cohort.

[b] Cox proportional hazards models were used to estimate the associations between: 1) carvedilol versus metoprolol tartrate initiation and 1-year all-cause mortality; and 2) carvedilol versus metoprolol succinate initiation and 1-year all-cause mortality.

[c] Fine and Gray proportional subdistribution hazards models were used to estimate the associations between: 1) carvedilol versus metoprolol tartrate initiation and 1-year all-cause mortality; and 2) carvedilol versus metoprolol succinate initiation and 1-year all-cause mortality. Non-cardiovascular death was treated as a competing risk.

[d] Adjusted analyses controlled for all variables listed in Table 6.2 using inverse probability of treatment weighting.

Abbreviations: CI, confidence interval; HR, hazard ratio; no., number; p-y, person-years; ref., referent

Table 6.6 Association between carvedilol versus metoprolol initiation and 1-year mortality among patients with the low-income subsidy benefit: intent-to-treat analysis[a]

Patients with the low-income subsidy benefit (n = 20,783)									
		1-year all-cause mortality[b]				1-year cardiovascular mortality[c]			
Beta blocker	n	No. events (%)	Rate per 1,000 p-y	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[d]	No. events (%)	Rate per 1,000 p-y	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[d]
Metoprolol	13,524	1,937 (14.3%)	181.5	1.00 (ref.)	1.00 (ref.)	841 (6.2%)	78.8	1.00 (ref.)	1.00 (ref.)
Carvedilol	7,259	1,162 (16.0%)	209.8	1.15 (1.07, 1.24)	1.10 (1.02, 1.19)	567 (7.8%)	102.4	1.29 (1.16, 1.44)	1.23 (1.10, 1.36)

An intent-to-treat design was employed in all analyses.

[a] Patient counts, event counts (% of patients) and event rates presented are from the unweighted cohort.

[b] Cox proportional hazards models were used to estimate the associations between: 1) carvedilol versus metoprolol tartrate initiation and 1-year all-cause mortality; and 2) carvedilol versus metoprolol succinate initiation and 1-year all-cause mortality.

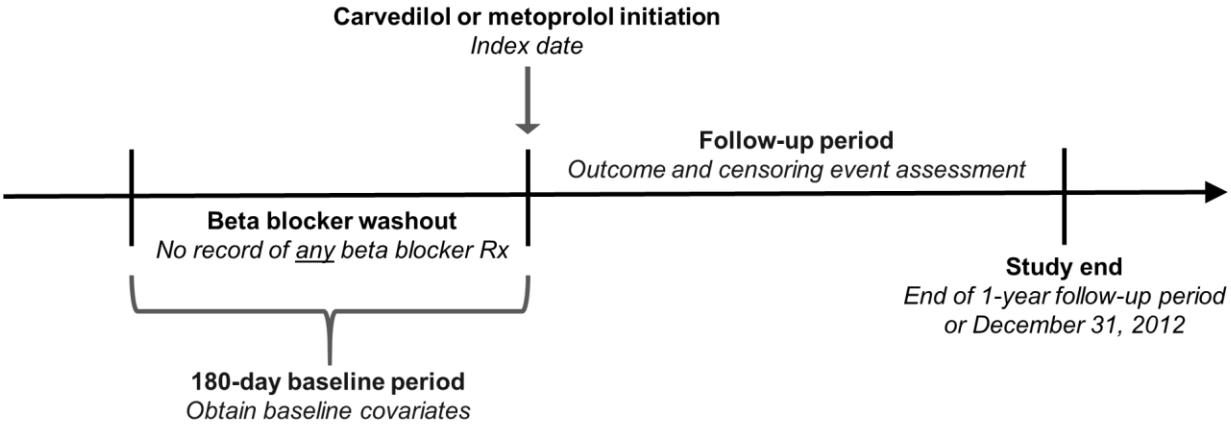
[c] Fine and Gray proportional subdistribution hazards models were used to estimate the associations between: 1) carvedilol versus metoprolol tartrate initiation and 1-year all-cause mortality; and 2) carvedilol versus metoprolol succinate initiation and 1-year all-cause mortality. Non-cardiovascular death was treated as a competing risk.

[d] Adjusted analyses controlled for all variables listed in Table 6.2 using inverse probability of treatment weighting.

Abbreviations: CI, confidence interval; HR, hazard ratio; no., number; p-y, person-years; ref., referent

Figures

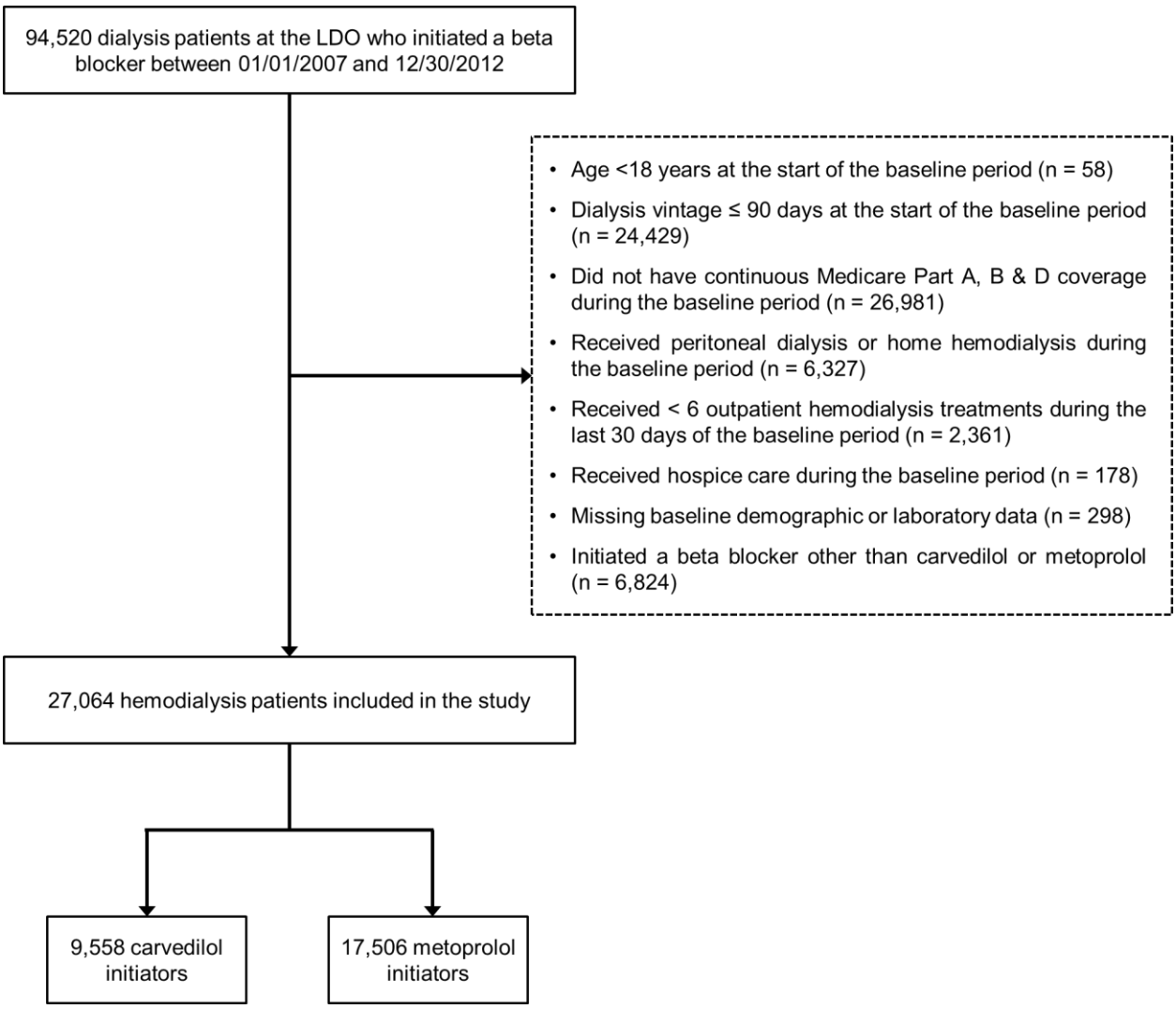
Figure 6.1 Aim 3 study design



Carvedilol and metoprolol initiators were defined as hemodialysis patients who had no record of a beta blocker prescription in the previous 180 days (beta blocker washout period). Among these patients, the index date was defined as the date of carvedilol or metoprolol initiation. Baseline covariates were identified in the 180-day period prior to the index date. Study follow-up began immediately after the index date.

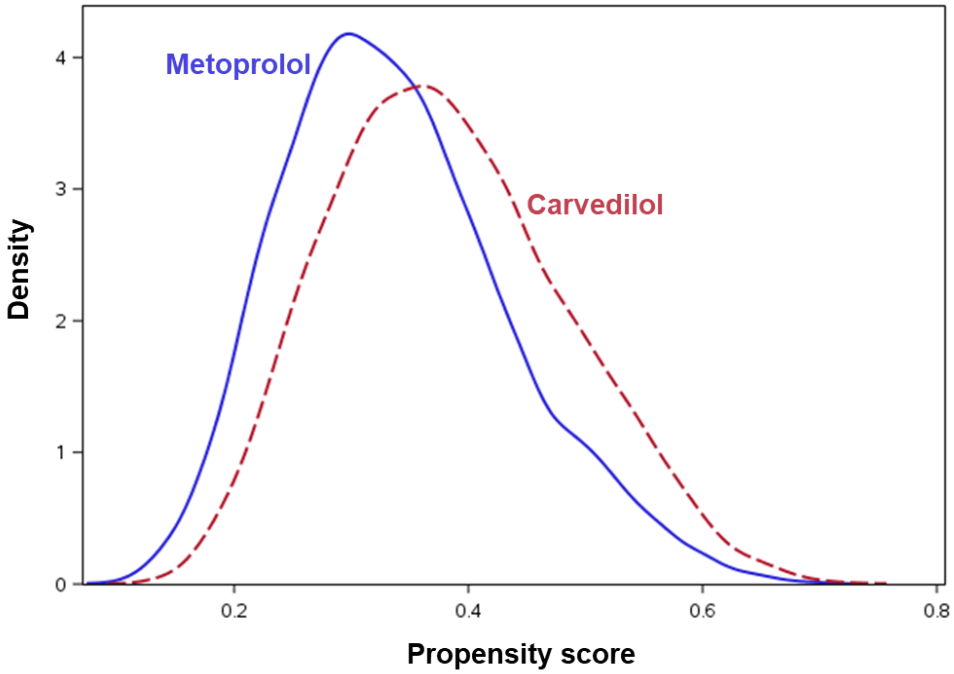
Abbreviations: Rx, prescription

Figure 6.2 Flow diagram depicting the assembly of the Aim 3 study cohort



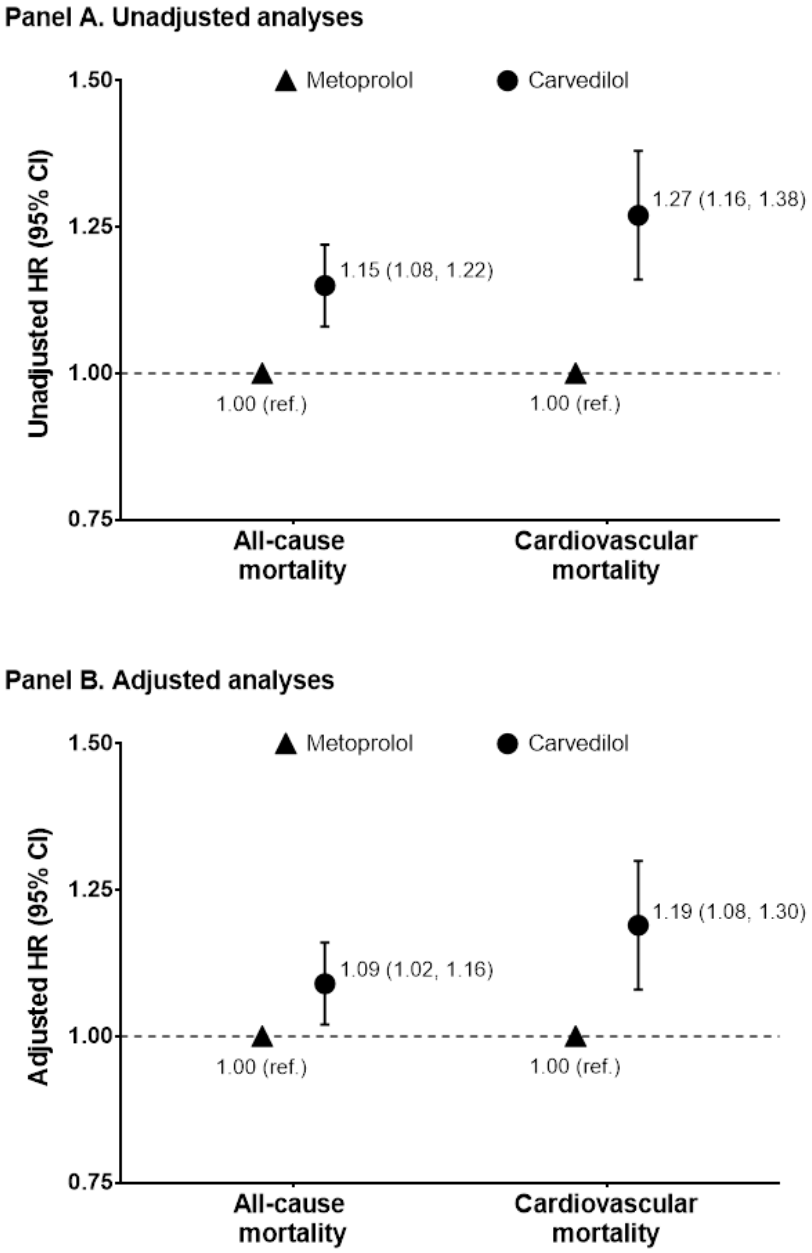
Abbreviations: LDO, large dialysis organization

Figure 6.3 Propensity score distribution of patients treated with carvedilol and metoprolol



The blue solid line represents the propensity score distribution among metoprolol initiators. The red dashed line represents the propensity score distribution of carvedilol initiators.

Figure 6.4 Association between carvedilol versus metoprolol initiation and 1-year mortality: intent-to-treat analysis



An intent-to-treat design was employed in all analyses. Cox proportional hazards models were used to estimate the association between carvedilol (versus metoprolol) initiation and 1-year all-cause mortality. Fine and Gray proportional subdistribution hazards models were used to estimate the association between carvedilol (versus metoprolol) initiation and 1-year cardiovascular mortality. In cardiovascular mortality analyses, non-cardiovascular death was treated as a competing risk. Inverse probability of treatment weighting was used in adjusted analyses to control for all the baseline covariates variables listed in Table 6.2.

Abbreviations: CI, confidence interval; HR, hazard ratio; ref., referent

CHAPTER 7: CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Aim 1: Patterns of beta blocker use

While this patterns of use study was conducted to inform Aims 2 and 3 of this dissertation, it does have broader implications. In a cohort of maintenance hemodialysis patients, we demonstrated that the utilization of beta blocker medications after index therapy initiation was dynamic. Both discontinuation and therapy re-initiation were common. When tracking beta blocker utilization post-index date with pharmacy claims data, making the assumption that patients continued beta blocker therapy during hospital and skilled nursing facility admissions resulted in lower estimated rates of beta blocker discontinuation as compared to rates of discontinuation based upon prescription fill information alone, regardless of the grace period used to define discontinuation. These findings suggest that administrative claims-based studies assessing the patterns of use of chronic disease medications, such as beta blocker therapy, in the hemodialysis population should consider accounting for hospital and skilled nursing facility admissions when assessing chronic disease medication use longitudinally.

Aim 2: Beta blocker adherence and mortality

Typically, PDC is calculated using pharmacy claims data by adding the number of days that a patient has prescription medication available to them (based on the date a prescription was dispensed and its days supply) during a set period of observation, divided by the number of days in the observation period. This standard approach for calculating PDC approach ignores time periods that patients spent in the hospital or a skilled nursing facility. In these settings, chronic

disease medications, such as beta blockers, are often provided to patients by hospital inpatient or skilled nursing facility pharmacies. During these admissions, prescription insurance-based home medication supplies are not utilized. Thus, in populations with high rates of hospital and skilled nursing facility admissions (e.g. hemodialysis patients), the standard PDC metric may misestimate the time patients have chronic disease medications available to them. In this dissertation aim, we found that the proportion of patients considered adherent to beta blocker therapy (PDC $\geq$ 80%) was lower when the standard PDC metric was employed as compared to a modified PDC metric that accounted for time spent in the hospital or skilled nursing facility. These results indicate that the classification of patients into adherent and non-adherent categories varies depending on the PDC metric used. Furthermore, we found that patients who were adherent to beta blocker therapy (PDC $\geq$ 80%) as compared to those who were non-adherent (PDC < 80%) had lower rates of all-cause mortality, regardless of the PDC metric used. However, notably, when modified (versus standard) beta blocker PDC was used to determine beta blocker adherence the observed adherence—mortality association was attenuated.

Our results suggest that it may be important to consider time periods spent in the hospital or a skilled nursing facility when PDC metrics are used to evaluate the study medication adherence—mortality associations, especially in populations that experience high rates of the aforementioned admission types (e.g. hemodialysis patients). Further research evaluating the impact of the adherence adjustment method used in this dissertation is warranted.

Aim 3: Comparative study of carvedilol versus metoprolol initiation and mortality

To our knowledge, this dissertation aim was the first investigation evaluating the comparative mortality risk of carvedilol and metoprolol therapy among individuals receiving maintenance hemodialysis. We demonstrated that carvedilol (versus metoprolol) initiation was

associated with increased 1-year all-cause and cardiovascular mortality. The observed associations were consistent within clinically relevant subgroups and robust across several sensitivity analyses. Data from our *post hoc* analysis indicate that one potential mechanism for the observed mortality associations may be an increased rate of intradialytic hypotension after carvedilol (versus metoprolol) initiation. Our results suggest that clinicians should consider potential adverse hemodynamic effects of carvedilol (versus metoprolol) when selecting between these beta blockers in hemodialysis patients. It may be reasonable to consider metoprolol initiation (over carvedilol) among individuals at high risk for intradialytic hypotension. Alternatively, it may be prudent to recommend that patients hold carvedilol doses prior to hemodialysis in order to minimize its intradialytic hypotensive effects. Given the unique pharmacokinetic and hemodynamic considerations in the ESRD population, additional study of the efficacy and safety of beta blockers, as well as other cardioprotective medications with antihypertensive properties is needed.

More broadly speaking, the results of this dissertation aim illustrates the importance of evaluating the safety and effectiveness of medications among hemodialysis patients, a special population with unique drug dosing considerations. In the absence of clinical trial data, large-scale, comparative effectiveness/safety studies will be needed to provide critical evidence to guide medication prescribing in ESRD. Furthermore, based on our findings and the results of other observational studies,[46] dialytic medication clearance appears to be an important consideration when evaluating the risk-benefit profiles of medications in the hemodialysis population. While resources describing the extent of medication dialyzablity are available to the nephrology community,[92, 93] the information contained in these references is dated. Available hemodialysis-based pharmacokinetic data is often derived from studies conducted in an era prior to the development and utilization of modern high-flux/high-efficiency dialysis membranes. Currently,

there is a lack of available data describing the effect of renal replacement therapy on drug disposition under the dialysis treatment conditions of contemporary clinical practice. Thus, additional research aimed at determining the dialyzablity of medications commonly used by hemodialysis patients and the corresponding impact on patient outcomes is warranted.

APPENDIX: SUPPLEMENTAL MATERIAL

Supplemental Table 1. Baseline covariate definitions used in Aims 1, 2 and 3

DEMOGRAPHICS AND PATIENT CHARACTERISTICS		
Covariate	**Description and definition**	**Data source**
Age	Age in years at the start of the baseline period	USRDS Patients
Sex	Patient sex Categories Male (ref.) Female	USRDS Patients
Race	Patient race Categories White (ref.) Black Other	USRDS Patients
Hispanic ethnicity	Patient is Hispanic? Categories No (ref.) Yes	USRDS Patients
Low-income subsidy	Patient has Medicare Part D low-income subsidy coverage on the last day of the baseline period? Categories No (ref.) Yes	USRDS Medicare Part D
Year of index beta blocker was prescribed	Calendar year in which index beta blocker prescription was filled Categories 2007(ref.) 2008 2009 2010 2011 2012	USRDS Medicare Part D
Cause of end-stage renal disease (ESRD)	Cause of ESRD Categories Diabetes (ref.) Hypertension Glomerular disease Other	USRDS Medical Evidence Form
Body mass index	Body mass index determined using: 1) last non-missing height during the baseline period; and 2) average post-dialysis weight during the last 30 days of the baseline period Computed as: weight in kg/(height in meters)^2	Large Dialysis Organization (LDO) Treatment (weight) and Cohort (height) files

	Categories Underweight -- BMI <18.5 kg/m^2 Normal -- BMI of 18.50 to <25 kg/m^2 (ref.) Overweight -- BMI of 25 to <30 kg/m^2 Obese -- BMI ≥30 kg/m^2	
History of ≥1 renal transplant	History of at least 1 renal transplant (transplant occurred prior to the baseline period)? Categories No (ref.) Yes	USRDS Transplant
Dialysis vintage	Dialysis vintage as of the last day of the baseline period? Categories < 1 year 1 to 1.9 years (ref.) 2 to 2.9 years ≥3 years	USRDS Medical Evidence Form
COMORBID CONDITIONS[a]		
Covariate	**Description and definition**	**Data source**
Atrial fibrillation	Patient has atrial fibrillation? ICD-9 diagnosis code(s): 427.3 Categories No (ref.) Yes	USRDS Part A/B claims
Other arrhythmia	Patient has other (non-atrial fibrillation) arrhythmias? ICD-9 diagnosis code(s): 427.0–427.2, 427.4–427.9 Categories No (ref.) Yes	USRDS Part A/B claims
Angina	Patient has angina? ICD-9 diagnosis code(s): 413 Categories No (ref.) Yes	USRDS Part A/B claims
Cancer	Patient has a history of Cancer? ICD-9 diagnosis code(s): 140–149, 150–159, 160–169, 170–176, 179–189, 190-199, 200–208, 209.0–209.3, 209.7, 230-234 Categories No (ref.) Yes	USRDS Part A/B claims

Conduction disorder	Patient has a conduction disorder? ICD-9 diagnosis code(s): 426 Categories No (ref.) Yes	USRDS Part A/B claims
Chronic obstructive pulmonary disease (COPD)/asthma	Patient has COPD/asthma? ICD-9 diagnosis code(s): 491–494, 496 Categories No (ref.) Yes	USRDS Part A/B claims
Coronary atherosclerosis	Patient has coronary atherosclerosis? ICD-9 diagnosis code(s): 414.0–414.4 Categories No (ref.) Yes	USRDS Part A/B claims
Diabetes	Patient has diabetes? ICD-9 diagnosis code(s): 250 Categories No (ref.) Yes	USRDS Part A/B claims
Gastrointestinal (GI) bleed	Patient had a GI bleed? ICD-9 diagnosis code(s): 456.0–456.2, 530.7, 531–534, 569.84, 569.85, 578 Categories No (ref.) Yes	USRDS Part A/B claims
Heart failure	Patient has heart failure? ICD-9 diagnosis code(s): 398.91, 402.x1, 404.x1, 404.x3, 428 Categories No (ref.) Yes	USRDS Part A/B claims
Hypertension	Patient has hypertension? ICD-9 diagnosis code(s): 401–405 Categories No (ref.) Yes	USRDS Part A/B claims
Liver disease	Patient has liver disease (including hepatitis B, hepatitis C and chronic liver disease)? ICD-9 diagnosis code(s): 070.2–070.3, 070.41, 070.44, 070.51, 070.54, 070.7, 571 Categories No (ref.)	USRDS Part A/B claims

	Yes	
Myocardial infarction	Patient had a myocardial infarction? ICD-9 diagnosis code(s): 410 Categories No (ref.) Yes	USRDS Part A/B claims
Peripheral artery disease	Patient has peripheral artery disease? ICD-9 diagnosis code(s): 440–441, 443–444, 447, 451–453, 557 Categories No (ref.) Yes	USRDS Part A/B claims
Stroke	Patient has a history of stroke? ICD-9 diagnosis code(s): 430–438 Categories No (ref.) Yes	USRDS Part A/B claims
Valvular disease	Patient has valvular disease? ICD-9 diagnosis code(s): 394–396, 424 Categories No (ref.) Yes	USRDS Part A/B claims
History of non-compliance	Patient has a history of non-compliance? ICD-9 diagnosis code(s): V15.81, V45.12 Categories No (ref.) Yes	USRDS Part A/B claims
	DIALYSIS TREATMENT	
Covariate	**Description and definition**	**Data source**
Vascular access	Last non-missing vascular access used during the baseline period Categories Fistula (ref.) Graft Catheter	LDO Treatment and Access files
Interdialytic weight gain	Average interdialytic weight gain in the last 30 days of the baseline period Categories <3 kg (ref.) ≥3 kg	LDO Treatment file

Delivered dialysis treatment time	Average delivered treatment time in the last 30 days of the baseline period Categories <240 min ≥240 min (ref.)	LDO Treatment file
Pre-dialysis systolic blood pressure	Average pre-dialysis systolic blood pressure during the last 30 days of the baseline period Categories <130 mmHg 130 – 149 mmHg (ref.) 150 – 169 mmHg ≥170 mmHg	LDO Treatment file
Recent history of intradialytic hypotension	Had an intradialytic nadir systolic blood pressure <90 mmHg in at least 30% of dialysis treatments in the last 30 days of the baseline period?[57] Categories No (ref.) Yes	LDO Treatment file
Recent history of intradialytic hypertension	Had a pre- to post-dialysis systolic BP rise >0 mmHg[94] in at least 30% of dialysis treatments in the last 30 days of the baseline period? Categories No (ref.) Yes	LDO Treatment file
LABORATORY		
Covariate	**Description and definition**	**Data source**
Albumin	Last non-missing albumin measurement during the baseline period Categories ≤3 g/dL 3.1 –4.0 >4.0 g/dL (ref.)	LDO Lab file
Calcium	Last non-missing corrected calcium measurement during the baseline period Categories <8.5 mg/dL 8.5 – 10.2 mg/dL (ref.) >10.2 mg/dL	LDO Labs file
Phosphorus	Last non-missing serum phosphorus measurement during the baseline period Categories <3.5 mg/dL 3.5 – 5.5 mg/dL (ref.) >5.5 mg/dL	LDO Labs file

Potassium	Last non-missing potassium during the baseline period Categories <4 mEq/L 4-6 mEq/L (ref.) >6 mEq/L	LDO Labs file
Hemoglobin	Last non-missing hemoglobin during the baseline period Categories <9.5 g/dL 9.5-12 g/dL >12 g/dL	LDO Labs file
eKt/v	Last non-missing eKt/V during the baseline period Categories <1.2 ≥1.2 (ref.)	LDO Labs file
	MEDICATION USE	
Covariate	**Description and definition**	**Data source**
Number of baseline medications	Number of prescription medications used in the last 30 days of the baseline period	USRDS Medicare Part D claims
Alpha blocker	Use of an alpha blocker in the last 30 days of the baseline period? Categories No (ref.) Yes	USRDS Medicare Part D claims
Angiotensin converting enzyme (ACE) inhibitor	Use of an ACE inhibitor in the last 30 days of the baseline period? Categories No (ref.) Yes	USRDS Medicare Part D Claims
Angiotensin receptor blocker (ARB)	Use of an ARB in the last 30 days of the baseline period? Categories No (ref.) Yes	USRDS Medicare Part D Claims
Calcium channel blocker	Use of a calcium channel blocker in the last 30 days of the baseline period? Categories No (ref.) Yes	USRDS Medicare Part D Claims

Central alpha agonist	Use of a central alpha agonist in the last 30 days of the baseline period? Categories No (ref.) Yes	USRDS Medicare Part D Claims
Diuretic	Use of a diuretic in the in the last 30 days of the baseline period? Categories No (ref.) Yes	USRDS Medicare Part D Claims
Vasodilator	Use of a vasodilator in the last 30 days of the baseline period? Categories No (ref.) Yes	USRDS Medicare Part D Claims
Statin	Use of a statin in the last 30 days of the baseline period? Categories No (ref.) Yes	USRDS Medicare Part D Claims
Other cholesterol medication	Use of another non-statin cholesterol medication (including bile acid sequestrants, cholesterol absorption inhibitors, fibrates or niacin) in the last 30-days of baseline? Categories No (ref.) Yes	USRDS Medicare Part D Claims
Digoxin	Use of digoxin in the last 30 days of the baseline period? Categories No (ref.) Yes	USRDS Medicare Part D Claims
Long-acting nitrate	Use of a long-acting nitrate in the last 30 days of the baseline period? Categories No (ref.) Yes	USRDS Medicare Part D Claims
Antiplatelet	Use of an antiplatelet medication in the last 30 days of the baseline period? Categories No (ref.) Yes	USRDS Medicare Part D Claims
Anticoagulant	Use of an anticoagulant medication in the last 30 days of the baseline period?	USRDS Medicare Part D Claims

	Categories No (ref.) Yes	
Midodrine	Use of midodrine in the last 30 days of the baseline period? Categories No (ref.) Yes	USRDS Medicare Part D Claims
Use of ≥1 potent inhibitor of CYP2D6	Use of ≥1 medication that is a potent inhibitor of CYP2D6 (including amiodarone, bupropion, chloroquine, cinacalcet, diphenhydramine, fluoxetine, haloperidol, imatinib, paroxetine, propafenone, propoxyphene, quinidine, terbinafine or thioridazine) in the last 30 days of the baseline period? Categories No (ref.) Yes	USRDS Medicare Part D Claims

[a] Relevant administrative claims-based covariates were identified in the 180-day baseline period using USRDS data. For comorbidities specified in the table, each clinical condition of interest was identified using USRDS Medicare Part A and B claims. Comorbid conditions were considered present if an applicable ICD-9 discharge code (located in any position) was associated with at least one inpatient, home health, or skilled nursing facility claim during the 180-day baseline period; or if an applicable ICD-9 code (located in any position) was identified in ≥2 outpatient, physician/supplier or dialysis claims separated by at least 7 days during the 180-day baseline period. Specified three digit ICD-9 diagnosis categories include all existing 4th and 5th digit diagnosis codes. Specified four digit ICD-9 diagnosis categories include all existing 5th digit diagnosis codes.

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; GI, gastrointestinal; ICD-9, International Classification of Diseases, Ninth Revision;

REFERENCES

1. U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013.

2. Coca SG, Krumholz HM, Garg AX, Parikh CR. Underrepresentation of renal disease in randomized controlled trials of cardiovascular disease. *JAMA.* 2006;296:1377-1384.

3. Konstantinidis I, Nadkarni GN, Yacoub R, et al. Representation of Patients With Kidney Disease in Trials of Cardiovascular Interventions: An Updated Systematic Review. *JAMA Intern Med.* 2016;176:121-124.

4. Levin NW, Kotanko P, Eckardt KU, et al. Blood pressure in chronic kidney disease stage 5D-report from a Kidney Disease: Improving Global Outcomes controversies conference. *Kidney Int.* 2010;77:273-284.

5. St Peter WL, Sozio SM, Shafi T, et al. Patterns in blood pressure medication use in US incident dialysis patients over the first 6 months. *BMC Nephrol.* 2013;14:249.

6. Lopressor(R) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2008.

7. Toprol-XL (R) [package insert]. Wilmington, DE: AstraZeneca; 2008.

8. Coreg (R) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2008.

9. Tieu A, Velenosi T, Kucey AS, Weir MA, Urquhart B. Beta blocker pharmacokinetics and dialyzability in chronic hemodialysis patients [Abstract]. *J Am Soc Nephrol.* 2016;27:744A.

10. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;64:e139-228.

11. American College of Emergency P, Society for Cardiovascular A, Interventions, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a

report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;61:e78-140.

12. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;62:e147-239.

13. Messerli FH, Bangalore S, Julius S. Risk/benefit assessment of beta blockers and diuretics precludes their use for first-line therapy in hypertension. *Circulation.* 2008;117:2706-2715; discussion 2715.

14. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J.* 2007;28:1462-1536.

15. Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Mbewu A, Opie LH. Beta blockers for hypertension. *Cochrane Database Syst Rev.* 2012;11:CD002003.

16. Foley RN, Herzog CA, Collins AJ, United States Renal Data S. Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 Study. *Kidney Int.* 2002;62:1784-1790.

17. Goodkin DA, Young EW, Kurokawa K, Prutz KG, Levin NW. Mortality among hemodialysis patients in Europe, Japan, and the United States: case-mix effects. *Am J Kidney Dis.* 2004;44:16-21.

18. Winkelmayer WC, Patrick AR, Liu J, Brookhart MA, Setoguchi S. The increasing prevalence of atrial fibrillation among hemodialysis patients. *J Am Soc Nephrol.* 2011;22:349-357.

19. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2014;64:e1-76.

20. Goodkin DA, Bragg-Gresham JL, Koenig KG, et al. Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the

Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol.* 2003;14:3270-3277.

21. Zoccali C, Benedetto FA, Mallamaci F, et al. Prognostic impact of the indexation of left ventricular mass in patients undergoing dialysis. *J Am Soc Nephrol.* 2001;12:2768-2774.

22. Brophy JM, Joseph L, Rouleau JL. Beta blockers in congestive heart failure. A Bayesian meta-analysis. *Ann Intern Med.* 2001;134:550-560.

23. Cice G, Ferrara L, D'Andrea A, et al. Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. *J Am Coll Cardiol.* 2003;41:1438-1444.

24. Gilbert EM, Abraham WT, Olsen S, et al. Comparative hemodynamic, left ventricular functional, and antiadrenergic effects of chronic treatment with metoprolol versus carvedilol in the failing heart. *Circulation.* 1996;94:2817-2825.

25. Bristow MR. beta-adrenergic receptor blockade in chronic heart failure. *Circulation.* 2000;101:558-569.

26. Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ.* 1999;318:1730-1737.

27. Lopez-Sendon J, Swedberg K, McMurray J, et al. Expert consensus document on beta-adrenergic receptor blockers. *Eur Heart J.* 2004;25:1341-1362.

28. Frankenfield DL, Weinhandl ED, Powers CA, Howell BL, Herzog CA, St Peter WL. Utilization and costs of cardiovascular disease medications in dialysis patients in Medicare Part D. *Am J Kidney Dis.* 2012;59:670-681.

29. Lopes AA, Bragg-Gresham JL, Ramirez SP, et al. Prescription of antihypertensive agents to haemodialysis patients: time trends and associations with patient characteristics, country and survival in the DOPPS. *Nephrol Dial Transplant.* 2009;24:2809-2816.

30. Ranchord AM, Harding SA, Pidgeon G. Medications for the secondary prevention of ischaemic heart disease and heart failure are underutilized in dialysis patients. *Intern Med J.* 2008;38:361-364.

31. Sood MM, Battistella M, Lok CE. Patterns of cardioprotective medication prescription in incident hemodialysis patients. *Int Urol Nephrol.* 2009;41:1021-1027.

32. Miller LM, Hopman WM, Garland JS, Yeates KE, Pilkey RM. Cardioprotective medication use in hemodialysis patients. *Can J Cardiol.* 2006;22:755-760.

33. Roy P, Bouchard J, Amyot R, Madore F. Prescription patterns of pharmacological agents for left ventricular systolic dysfunction among hemodialysis patients. *Am J Kidney Dis.* 2006;48:645-651.

34. Andreucci VE, Fissell RB, Bragg-Gresham JL, et al. Dialysis Outcomes and Practice Patterns Study (DOPPS) data on medications in hemodialysis patients. *Am J Kidney Dis.* 2004;44:61-67.

35. Rahman M, Griffin V. Patterns of antihypertensive medication use in hemodialysis patients. *Am J Health Syst Pharm.* 2004;61:1473-1478.

36. Chow FY, Polkinghorne KR, Chadban SJ, Atkins RC, Kerr PG. Cardiovascular risk in dialysis patients: a comparison of risk factors and cardioprotective therapy between 1996 and 2001. *Nephrology (Carlton).* 2003;8:177-183.

37. Manley HJ, Bailie GR, Grabe DW. Comparing medication use in two hemodialysis units against national dialysis databases. *Am J Health Syst Pharm.* 2000;57:902-906.

38. Manley HJ, Garvin CG, Drayer DK, et al. Medication prescribing patterns in ambulatory haemodialysis patients: comparisons of USRDS to a large not-for-profit dialysis provider. *Nephrol Dial Transplant.* 2004;19:1842-1848.

39. Tozawa M, Iseki K, Iseki C, et al. Analysis of drug prescription in chronic haemodialysis patients. *Nephrol Dial Transplant.* 2002;17:1819-1824.

40. Trespalacios FC, Taylor AJ, Agodoa LY, Abbott KC. Incident acute coronary syndromes in chronic dialysis patients in the United States. *Kidney Int.* 2002;62:1799-1805.

41. Wetmore JB, Mahnken JD, Mukhopadhyay P, et al. Geographic variation in cardioprotective antihypertensive medication usage in dialysis patients. *Am J Kidney Dis.* 2011;58:73-83.

42. Wetmore JB, Mahnken JD, Rigler SK, et al. Impact of race on cumulative exposure to antihypertensive medications in dialysis. *Am J Hypertens.* 2013;26:234-242.

43. Molnar MZ, Gosmanova EO, Sumida K, et al. Predialysis Cardiovascular Disease Medication Adherence and Mortality After Transition to Dialysis. *Am J Kidney Dis.* 2016;68:609-618.

44. Agarwal R, Sinha AD, Pappas MK, Abraham TN, Tegegne GG. Hypertension in hemodialysis patients treated with atenolol or lisinopril: a randomized controlled trial. *Nephrol Dial Transplant.* 2014;29:672-681.

45. Roberts MA, Pilmore HL, Ierino FL, et al. The beta blocker to Lower Cardiovascular Dialysis Events (BLOCADE) Feasibility Study: A Randomized Controlled Trial. *Am J Kidney Dis.* 2016;67:902-911.

46. Weir MA, Dixon SN, Fleet JL, et al. β-blocker dialyzability and mortality in older patients receiving hemodialysis. *J Am Soc Nephrol.* 2015;26:987-996.

47. Shireman TI, Mahnken JD, Phadnis MA, Ellerbeck EF. Effectiveness comparison of cardio-selective to non-selective beta blockers and their association with mortality and morbidity in end-stage renal disease: a retrospective cohort study. *BMC Cardiovasc Disord.* 2016;16:60.

48. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis.* 2017;69:A7-A8.

49. Zebeta (R) [package insert]. Pomona, NY: Duramed Pharmaceuticals, Inc.; 2007.

50. Trandate (R) [package insert]. San Diego, CA: Prometheus Laboratories Inc.; 2010.

51. Bonet S, Agusti A, Arnau JM, et al. Beta-adrenergic blocking agents in heart failure: benefits of vasodilating and non-vasodilating agents according to patients' characteristics: a meta-analysis of clinical trials. *Arch Intern Med.* 2000;160:621-627.

52. Packer M, Antonopoulos GV, Berlin JA, Chittams J, Konstam MA, Udelson JE. Comparative effects of carvedilol and metoprolol on left ventricular ejection fraction in heart failure: results of a meta-analysis. *Am Heart J.* 2001;141:899-907.

53. Swedberg K, Olsson LG, Charlesworth A, et al. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta blockers: results from COMET. *Eur Heart J.* 2005;26:1303-1308.

54. Mrdovic IB, Savic LZ, Perunicic JP, et al. Randomized active-controlled study comparing effects of treatment with carvedilol versus metoprolol in patients with left ventricular dysfunction after acute myocardial infarction. *Am Heart J.* 2007;154:116-122.

55. Jonsson G, Abdelnoor M, Muller C, Kjeldsen SE, Os I, Westheim A. A comparison of the two beta blockers carvedilol and atenolol on left ventricular ejection fraction and clinical endpoints after myocardial infarction. a single-centre, randomized study of 232 patients. *Cardiology.* 2005;103:148-155.

56. Katritsis DG, Panagiotakos DB, Karvouni E, et al. Comparison of effectiveness of carvedilol versus bisoprolol for maintenance of sinus rhythm after cardioversion of persistent atrial fibrillation. *Am J Cardiol.* 2003;92:1116-1119.

57. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol.* 2015;26:724-734.

58. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol.* 2009;4:914-920.

59. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. *Clin J Am Soc Nephrol.* 2009;4:1925-1931.

60. Shafi T, Jaar BG, Plantinga LC, et al. Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. *Am J Kidney Dis.* 2010;56:348-358.

61. McIntyre CW, Harrison LE, Eldehni MT, et al. Circulating endotoxemia: a novel factor in systemic inflammation and cardiovascular disease in chronic kidney disease. *Clin J Am Soc Nephrol.* 2011;6:133-141.

62. Eldehni MT, Odudu A, McIntyre CW. Randomized clinical trial of dialysate cooling and effects on brain white matter. *J Am Soc Nephrol.* 2015;26:957-965.

63. Stefansson BV, Brunelli SM, Cabrera C, et al. Intradialytic hypotension and risk of cardiovascular disease. *Clin J Am Soc Nephrol.* 2014;9:2124-2132.

64. Chou JA, Streja E, Nguyen DV, et al. Intradialytic hypotension, blood pressure changes and mortality risk in incident hemodialysis patients. *Nephrol Dial Transplant.* 2017.

65. Hahn L, Hahn M. Carvedilol-induced hyperkalemia in a patient with chronic kidney disease. *J Pharm Pract.* 2015;28:107-111.

66. Griffith TF, Chua BS, Allen AS, Klassen PS, Reddan DN, Szczech LA. Characteristics of treated hypertension in incident hemodialysis and peritoneal dialysis patients. *Am J Kidney Dis.* 2003;42:1260-1269.

67. Berger AK, Duval S, Krumholz HM. Aspirin, beta blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction. *J Am Coll Cardiol.* 2003;42:201-208.

68. Abbott KC, Trespalacios FC, Agodoa LY, Taylor AJ, Bakris GL. beta blocker use in long-term dialysis patients: association with hospitalized heart failure and mortality. *Arch Intern Med.* 2004;164:2465-2471.

69. Ishani A, Herzog CA, Collins AJ, Foley RN. Cardiac medications and their association with cardiovascular events in incident dialysis patients: cause or effect? *Kidney Int.* 2004;65:1017-1025.

70. Winkelmayer WC, Charytan DM, Levin R, Avorn J. Poor short-term survival and low use of cardiovascular medications in elderly dialysis patients after acute myocardial infarction. *Am J Kidney Dis.* 2006;47:301-308.

71. Pun PH, Lehrich RW, Smith SR, Middleton JP. Predictors of survival after cardiac arrest in outpatient hemodialysis clinics. *Clin J Am Soc Nephrol.* 2007;2:491-500.

72. Nakao K, Makino H, Morita S, et al. Beta blocker prescription and outcomes in hemodialysis patients from the Japan Dialysis Outcomes and Practice Patterns Study. *Nephron Clin Pract.* 2009;113:c132-139.

73. Tangri N, Shastri S, Tighiouart H, et al. beta blockers for prevention of sudden cardiac death in patients on hemodialysis: a propensity score analysis of the HEMO Study. *Am J Kidney Dis.* 2011;58:939-945.

74. Kitchlu A, Clemens K, Gomes T, et al. Beta blockers and cardiovascular outcomes in dialysis patients: a cohort study in Ontario, Canada. *Nephrol Dial Transplant.* 2012;27:1591-1598.

75. Matsue Y, Suzuki M, Nagahori W, Ohno M, Matsumura A, Hashimoto Y. Beta blocker prevents sudden cardiac death in patients with hemodialysis. *Int J Cardiol.* 2013;165:519-522.

76. Tang Y, Brooks JM, Wetmore JB, Shireman TI. Association between higher rates of cardioprotective drug use and survival in patients on dialysis. *Res Social Adm Pharm.* 2015;11:824-843.

77. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol.* 2003;158:915-920.

78. DiMatteo MR, Giordani PJ, Lepper HS, Croghan TW. Patient adherence and medical treatment outcomes: a meta-analysis. *Med Care.* 2002;40:794-811.

79. Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. *Health Aff (Millwood).* 2011;30:91-99.

80. Austin PC. Using the Standardized Difference to Compare the Prevalence of a Binary Variable Between Two Groups in Observational Research. *Communications in Statistics - Simulation and Computation.* 2009;38:1228-1234.

81. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association.* 1999;94:496-509.

82. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol.* 2008;168:656-664.

83. Manley HJ, Cannella CA, Bailie GR, St Peter WL. Medication-related problems in ambulatory hemodialysis patients: a pooled analysis. *Am J Kidney Dis.* 2005;46:669-680.

84. United States Renal Data System. ESRD Analytic Methods. [https://www.usrds.org/2016/view/v2_00_appx.aspx] Accessed 11 Jul 2017. Vol 2017.

85. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. *Am J Epidemiol.* 2006;163:1149-1156.

86. Briasoulis A, Palla M, Afonso L. Meta-analysis of the effects of carvedilol versus metoprolol on all-cause mortality and hospitalizations in patients with heart failure. *Am J Cardiol.* 2015;115:1111-1115.

87. K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis.* 2005;45:S1-153.

88. Kooman J, Basci A, Pizzarelli F, et al. EBPG guideline on haemodynamic instability. *Nephrol Dial Transplant.* 2007;22 Suppl 2:ii22-44.

89. Mactier R, Hoenich N, Breen C. UK Renal Association clinical practice guidelines: haemodialysis. http://www.renal.org/guidelines/modules/haemodialysis#sthash.eBdbSrRk.dpbs, 2009. [Accessed 23 Dec 2016].

90. Chang TI, Paik J, Greene T, et al. Intradialytic hypotension and vascular access thrombosis. *J Am Soc Nephrol.* 2011;22:1526-1533.

91. . In: Velentgas P, Dreyer NA, Nourjah P, Smith SR, Torchia MM, eds. *Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide*. Rockville (MD)2013.

92. Bailie G.R., MasonN.A. 2016 Dialysis of Drugss. Saline,Michigan: Renal Pharmacy Consultants, LLC, 2016.

93. Bennett WM. *Drug prescribing in renal failure : dosing guidelines for adults and children.* 5th ed. Philadelphia: American College of Physicians; 2007.

94. Park J, Rhee CM, Sim JJ, et al. A comparative effectiveness research study of the change in blood pressure during hemodialysis treatment and survival. *Kidney Int.* 2013;84:795-802.