RETROSPECTIVE ANALYSIS OF PRESCRIPTION DRUG CLAIMS, WITH APPLICATIONS TO RISK SCORE CONSTRUCTION AND TREATMENT OF HEART FAILURE IN END STAGE RENAL DISEASE

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Chapter 1

Introduction

Chronic kidney disease (CKD) is defined by either kidney damage or a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 for at least three months; kidney damage may be marked by pathological abnormalities, abnormalities in composition of blood (*e.g.*, elevated serum creatinine) or urine (*e.g.*, proteinuria), or abnormalities in imaging tests. By convention, CKD is classified into five stages of severity.[1] Stage 1 is defined by kidney damage accompanied by either normal or elevated GFR (*i.e.*, $\geq$ 90 mL/min/1.73 m^2) and stage 2 is defined by damage accompanied by modestly decreased GFR (*i.e.*, 60-89 mL/min/1.73 m^2). The large majority of patients in CKD Stage 1 or 2 will never progress to kidney failure. In contrast to CKD Stages 1 and 2, latter stages are defined exclusively by level of GFR. Stages 3 and 4 are defined by GFR between 30 and 59 ml/min/1.73 m^2 and between 15 and 29 mL/min/1.73 m^2, respectively. Finally, Stage 5 is defined either by GFR less than 15 ml/min/1.73 m^2 (usually accompanied by the symptoms of uremia) or by need for initiation of renal replacement therapy (*i.e.*, dialysis or kidney transplant).

End stage renal disease (ESRD) is defined by the complete or nearly complete failure of the kidneys to function. ESRD typically occurs when CKD has worsened to the point at which kidney function is less than 10% of normal. In incident ESRD cases from 2010 to 2012 (N = 335,334), mean estimated GFR, by the CKD-EPI equation, was 10.3 mL/min/1.73 m^2 at ESRD onset.[2] Ongoing survival with ESRD requires renal replacement therapy, in the form of either hemodialysis (HD), peritoneal dialysis (PD), or kidney transplant. In HD, a machine filters wastes, salts, and fluid from the blood.

Hemodialysis is the most common treatment modality for ESRD in the US, although site (*e.g.*, in a facility or at home) and schedule (*e.g.*, thrice-weekly or daily) of treatment may vary. In PD, a patient (or a machine) uses a catheter to fill the abdominal cavity with a manufactured solution (*i.e.*, dialysate), and waste products and excess fluid move via diffusion and osmosis, respectively, across the peritoneum from blood vessels to the solution. Despite considerable uncertainty regarding the comparative effectiveness of PD and HD, PD is currently relatively infrequently used in the US, with more than 10 HD patients for each PD patient in the prevalent ESRD population.[2] In kidney transplant, an allograft from a deceased or living donor is implanted in the patient. Risk of death is generally lower for kidney transplant versus dialysis, but treatment with transplant requires permanent immunosuppression. In 2012, there were 17,330 kidney transplants in the US, with 11,710 (67.6%) from deceased donors and 5,620 (34.3%) from living donors.[2] Use of this modality is constrained by availability of organs.

Patients undergoing chronic dialysis are eligible for Medicare enrollment, regardless of age, as codified by the Social Security Amendments of 1972.[3] However, the core elements of Medicare enrollment are the same for ESRD patients as for citizens who become eligible for Medicare due to elderly age. Specifically, Medicare Part A (hospital insurance) enrollment is premium-free, subject to satisfaction of conditions regarding work history or disability. For Medicare Part B (medical insurance) enrollment, patients must pay a monthly premium. In addition, Part B services require 20% co-insurance. This is a problematic expense for patients undergoing chronic dialysis, as dialysis itself is covered by Part B. In 2015, the base rate for outpatient dialysis covered by Medicare is $239.43 per session; that actual rate may be higher for medically complex patients.[4] On a

schedule of three sessions per week, co-insurance for dialysis alone totals nearly $150 (at minimum). To cover this expense, ESRD patients typically resort to one of two options. Patients with some assets may purchase Medicare Supplement Insurance (*i.e.*, Medigap), which covers co-insurance in exchange for a monthly premium. Patients with few or no assets may be concurrently enrolled in Medicare and Medicaid, the latter of which covers co-insurance for Part B services. Finally, as of 2006, patients may choose to enroll in Medicare Part D (prescription drug insurance). In fact, for patients who are concurrently enrolled in Medicare and Medicaid, enrollment in Medicare Part D is automatic and premium-free (unless a non-benchmark plan is selected). For patients who are enrolled in either Medicare Part A or Part B, but not in Medicaid, enrollment in Part D requires a monthly premium. These arcane details of Medicare eligibility suggest that many dialysis patients accumulate a tremendous volume of claims data regarding hospitalization, outpatient care (including outpatient dialysis), and prescription drug use.

Data arising from Medicare Part D are relatively new to researchers and hold tremendous potential for studies of comparative effectiveness. However, these data also present opportunities for novel methodologic studies. In ESRD patients, observational studies of the efficacy and safety of pharmacologic interventions are common, partially because patients with severe renal impairment have typically been excluded from randomized clinical trials of such interventions.[5] However, in the absence of randomization, the potential for unmeasured confounding exists. Particularly salient is confounding attributable to disease severity, as patients undergoing chronic dialysis vary substantially in medical complexity. ESRD patients may suffer from a wide variety of comorbid conditions. Identification of comorbidity in both prospective and retrospective

studies can be challenging and costly. Algorithms may lack either sensitivity or specificity. It has been proposed that prescription drug records may represent a robust alternative to classification of comorbidity from clinical assessment and medical record abstraction. In fact, with exhaustive data, one might design a *comorbidity score* (or more generally, a risk score) that grades disease severity according to use of particular medications. In the first study of this dissertation, I used Part D claims to construct and validate comorbidity scores for dialysis patients. Specifically, I constructed 4 comorbidity scores: 2 for incident dialysis patients and 2 for prevalent patients. For each set of patients, I construct scores corresponding to risks of death and hospitalization.

Chronic kidney disease and cardiovascular disease (CVD) are tightly intertwined, likely partially due to the role of hypertension in the pathogeneses of both CKD and CVD. In patients with CKD who have not progressed to ESRD, the burden of CVD is severe. In adult (*i.e.*, age $\geq$ 20 years) NHANES participants in 1999-2006, prevalence of CVD for patients with estimated GFR (from the CKD-EPI equation) $\geq$ 60, 45-59, 30-44, and < 30 mL/min/1.73 m^2 was 6.6%, 31.0%, 49.0%, and 63.0%, respectively.[6] A meta-analysis of 11 prospective studies that included 2138 patients with Type 2 diabetes reported that the odds ratio of cardiovascular morbidity and mortality for the presence of micro-albuminuria (*i.e.*, urinary albumin excretion [UAE] 30-300 mg/day) versus normal UAE was 2.0 (95% confidence interval, 1.4-2.7).[7] This association does not appear to be substantially modified by type of diabetes. In an analysis of elderly (*i.e.*, age $\geq$ 65 years) Medicare beneficiaries, the rate of hospitalization due to cardiovascular causes was 126.4 versus 87.9 admissions per 1000 patient-years for CKD versus no CKD, respectively, with CKD status ascertained from claims.[6] In addition, the predominant cause of death in

patients with CKD is CVD. In a systematic review of the association of (non-dialysis-dependent) CKD with risk of death, cardiovascular deaths constituted 58% of all deaths; in contrast, during the era from 1985 to 2005, which was contemporaneous with the reviewed studies, the percentage of US deaths due to cardiovascular causes steadily declined from 44.3% to 32.5%.[8]

The explanation for elevated risk of CVD in CKD is likely multifactorial. On one hand, prevalence of traditional risk factors for CVD is generally higher in CKD versus non-CKD patients. Prevalence of hypertension is very high. In subjects who satisfied initial screening criteria in the Modification of Diet in Renal Disease (MDRD) study, prevalence of hypertension (as indicated both from review of medical records and by use of antihypertensive medications) ranged from 66% in the highest decile of GFR (mean within-decile GFR, 83 mL/min/1.73 m^2) to 95% in the lowest decile of GFR (12 mL/min/1.73 m^2).[9] As one of the randomized interventions in the MDRD study was strict blood pressure control, one could speculate that volunteer bias resulted in exaggerated estimates of hypertensive prevalence. A later analysis of adult NHANES participants reported estimates of hypertension prevalence between 61% and 66% in those with estimated GFR < 60, regardless of estimation techniques (compared to about 25% in those with estimated GFR $\geq$ 60).[6] However, prevalence of hypertension likely varies according to degree of renal dysfunction, as the MDRD study suggested. In five studies of patients with Type 2 diabetes, the prevalence of hypertension (*i.e.*, systolic blood pressure [BP] > 140 or diastolic BP > 90 mm Hg) was between 40% and 83% in patients with micro-albuminuria and between 78% and 96% in patients with macro-albuminuria (*i.e.*, UAE > 300 mg/day).[10] Finally, dyslipidemia is common in CKD patients. In an

analysis of 16 studies of patients with nephrotic syndrome (*i.e.*, urinary protein excretion > 3 g/day), 88% of patients had total cholesterol > 240 mg/dL.[11]

On the other hand, non-traditional risk factors pertaining to renal insufficiency may play important roles in the pathogenesis of CVD. Persistent activation of the renin-angiotensin system (RAS), probably resulting from decreased blood flow into the glomeruli, may increase levels of angiotensin II, resulting in systemic vasoconstriction and stimulation of the sympathetic nervous system.[12] Insufficient filtration of sodium and chloride encourages water retention and may result in fluid overload, thereby increasing blood pressure and risk of heart failure.[13] Loss of renal function may result in derangements of calcium and phosphorus metabolism, as the kidneys produce too little calcitriol (*i.e.*, activated vitamin D) and retain too much phosphate, resulting in secondary hyperparathyroidism, as well as bone resorption and probable vascular calcification.[14] The kidney is also responsible for production of erythropoietin, which stimulates red blood cell production in the bone marrow, so loss of renal function typically results in anemia, which may lead to increased cardiac output and left ventricular hypertrophy.[15] Defects in immune response arise in the presence of renal dysfunction; higher risk of infection may alter the risk of CVD.[16-17] Finally, the accumulation of uremic toxins and subsequently increased oxidative stress may also place stress on cardiac tissue.

In patients who have progressed to ESRD, the pathophysiology of CVD is similar, but the risk is even higher. While cardiovascular causes constituted only 42.1% of all deaths in prevalent dialysis patients in 2006-2008 (because of increased competition from other causes, particularly infection), the absolute rate of 87.9 cardiovascular deaths per 1000 patient-years is far higher than in the US population (in which there were roughly

2.5 cardiovascular deaths per 100,000 people in 2007).[6] The hospitalization rate for cardiovascular causes in prevalent dialysis patients in 2006-2008 was a staggering 525 admissions per 1,000 years patient-years, although the rate represented a modest decline from the previous three-year interval (*i.e.*, in 2003-2005), in which there were 572 admissions per 1000 patient-years.[6] Mix of cardiovascular morbidity is varied. In an analysis of hypertensive dialysis patients who were alive after one year of dialysis (after having begun dialysis in 2003), the prevalence of heart failure was 36.4% and 31.9% in those with and without diabetes, respectively.[18] The prevalence of coronary heart disease and peripheral vascular disease were 12.5% and 13.7%, respectively, in patients with diabetes, while corresponding prevalence estimates were 9.8% and 9.6% in patients without diabetes.[18] Because the most common cause of death in dialysis patients is sudden cardiac death, arrhythmia could be anticipated. In a study of 74 patients, prevalence of complex ventricular arrhythmia was 50%.[19]

Heart failure is a clinical syndrome in which the heart is incapable of maintaining cardiac output adequate to meet metabolic requirements and accommodate venous return.[20] Heart failure is caused by a loss of functional myocardial cells after injury to the heart from any number of causes. In the US, most common etiologies are ischemic heart disease, hypertension, and diabetes; less common causes include dilated cardiomyopathy, infection, toxic insults (*e.g.*, alcohol), and valvular disease. Among dialysis patients in the US, ischemic events and diabetes are common causes of heart failure, but other unique etiologies are important.[21] Fluid overload between dialysis sessions and anemia (resulting in increased preload because of reduced blood viscosity) contribute to the pathogenesis of heart failure.

In the general population, the American Heart Association currently recommends several pharmacological interventions for patients with current or prior symptoms of heart failure and reduced left ventricular ejection fraction, including diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta blockers that have been found to reduce the risk of death (*i.e.*, bisoprolol, carvedilol, and extended-release metoprolol succinate), angiotensin II receptor blockers (ARBs) that are indicated in the treatment of heart failure (*i.e.*, candesartan, losartan, and valsartan), and aldosterone antagonists.[22] Prescription of diuretics to dialysis patients is mostly limited to loop diuretics in incident patients with residual renal function. Aldosterone antagonists, specifically spironolactone and eplerenone, are contraindicated in patients with renal insufficiency, because of increased risk of hyperkalemia, although recent data have questioned this prohibition.[23-24] Nevertheless, this leaves mainly ACE inhibitors, beta blockers, and ARBs in the armamentarium. Of course, ACE inhibitors and ARBs are closely related, as both inhibit the effects of the renin-angiotensin system. Whether ACE inhibitors and ARBs are efficacious for the treatment of heart failure in dialysis patients is unknown, although several small randomized clinical trials suggest therapeutic potential.[25-26] In the second study of this dissertation, I used Medicare claims data to conduct a retrospective cohort study of dialysis patients who had been discharged from hospitalization principally for heart failure. I compared risks of death and hospitalization in patients who were dispensed a renin-angiotensin system inhibitor shortly after discharge and matched control patients who were not dispensed such an inhibitor.

ACE inhibitors and ARBs constitute large subclasses of antihypertensive medications. Currently in the US, there are 10 ACE inhibitors and 8 ARBs that have been

approved by the Food and Drug Administration for human prescription. Some of these agents have been rigorously assessed for efficacy in randomized clinical trials of patients with heart failure (and possess indications that suggest as much), while many others have been assessed only for blood pressure control in patients with uncomplicated hypertension. Aside from questions about the evidence base underlying each of these agents, there are known differences in the absorption, distribution, metabolism, and excretion of these agents. For example, all ACE inhibitors (except fosinopril) are removed by hemodialysis, whereas ARBs are not removed by hemodialysis. Some agents have relatively short half-lives and are therefore dosed twice or thrice per day, while other agents have longer half-lives and are dosed once per day. These and other differences may have important pharmacodynamic implications. However, studies of the comparative effectiveness of individual ACE inhibitors and ARBs are few, likely primarily due to the challenge of achieving sufficient statistical power to detect effects that can be reasonably anticipated to be small in magnitude. In the third study of my dissertation, I compared risks of death and hospitalization associated with dispensation of benazepril, enalapril, lisinopril, ramipril, losartan, and valsartan to dialysis patients that had been discharged from hospitalization principally for heart failure. I also investigated features of medication use, including dosing, adherence, and persistence.

Chapter 2

Data Source

United States Renal Data System Database

The United States Renal Data System (USRDS) is a registry that collects, analyzes, and distributes information about end stage renal disease (ESRD) in the United States. The USRDS is operated by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in collaboration with the Centers for Medicare & Medicaid Services (CMS) and the Health Resources and Services Administration (HRSA). The USRDS manages a relational database that is updated annually and includes information about demographic characteristics of ESRD patients; measures of disease severity (*i.e.*, comorbid diagnoses and biochemical measurements) at the time of ESRD treatment initiation; longitudinal histories of treatment modalities and payors; and deaths. The database also include records of health care encounters, including hospitalizations, dialysis treatments, physician services, and prescription medications, although this information is limited to Medicare enrollees. The database represents a compilation of many sources, including CMS's Renal Management Information System (REMIS), the ESRD Network Organizations' Standard Information Management System (SIMS), Medicare Parts A and B claims, Medicare Part D events, the Organ Procurement and Transplantation Network (OPTN) database, and the Social Security Administration's Death Master File (DMF). Details concerning the linking and reconciling of these sources have been described elsewhere.[27] Key elements of the USRDS database are described in the following subsections.

ESRD Patient Profile

The ESRD patient profile enumerates all ESRD patients that have been identified by the USRDS since its inception in 1988. The profile includes a unique numeric identifier for each patient. The profile lists sex, ethnicity (Mexican Hispanic, non-Mexican Hispanic, non-Hispanic, or unknown), and race (white, black, Native American, Asian or Pacific Islander, other, or unknown). The profile also lists dates of birth, ESRD treatment initiation, and as applicable, death, kidney transplant(s), and kidney transplant failure(s). The primary source of mortality information is form CMS-2746 ("ESRD Death Notification"), which providers (*i.e.*, dialysis facilities and transplant centers) are required to submit within 2 weeks of the date of death. In addition to date of death, CMS-2746 includes the primary cause of death (as indicated by a three-digit code that specifies a particular cause in one of eight general categories: cardiac, vascular, infection, liver disease, gastrointestinal, metabolic, endocrine, or other), between zero and four secondary causes of death, and information about discontinuation of renal replacement therapy prior to death. CMS-2746 provides greater than 99% of mortality information for ESRD patients; the Social Security DMF provides the remainder, although the DMF does not include causes of death. Since 1994, dates of kidney transplant(s) are identified exclusively from the OPTN database, which is necessarily comprehensive in coverage of organ transplant events in the US. Dates of kidney transplant failure(s) are identified primarily from the OPTN database, and secondarily from SIMS and Medicare claims (as transplant failures not resulting in death necessitate dialysis treatment).

Medical Evidence Report Catalog

The Medical Evidence Report catalog contains all copies of form CMS-2728 ("End Stage Renal Disease Medical Evidence Report; Medicare Entitlement and/or Patient Registration"). CMS-2728 must be completed within 45 days of beginning renal replacement therapy in four cases: (1) patients who initiate dialysis as their first ESRD treatment modality; (2) patients who receive a kidney transplant as their first ESRD treatment modality; (3) patients who have been previously enrolled in Medicare and whose coverage was terminated at the conclusion of three years following a kidney transplant, but who are reapplying for Medicare coverage because of kidney transplant failure (thereby necessitating either the resumption of dialysis or a new kidney transplant); (4) patients who have been previously enrolled in Medicare and whose coverage was terminated at the conclusion of one year following cessation of dialysis, but who are reapplying for Medicare coverage because of either the resumption of dialysis or a new kidney transplant. Importantly, submission of CMS-2728 has been required for all such ESRD patients since April 1, 1995, regardless of any considerations regarding Medicare insurance. The form has undergone two major revisions, first in 1995 (when submission was mandated) and again in 2005.

The primary epidemiologic use of the catalog is the description of patients initiating treatment for ESRD (*i.e.*, incident ESRD patients). In this respect, the catalog includes several important elements. First, the catalog includes primary cause of renal failure, as indicated by a single diagnosis code from *The International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). While the 1995 and 2005 revisions of CMS-2728 specify 72 and 82 diagnosis codes as possible causes of renal

failure, respectively, the USRDS typically lists eight categories of primary cause (diabetes, hypertension, glomerulonephritis, cystic kidney disease, urological disease, other, or unknown) in its analysis, with an implicit acknowledgment that the pathologies of ESRD vary widely in patients with "other" primary causes. Second, the catalog includes height and dry weight, from which body mass index (BMI) can be calculated. Third, the catalog lists employment status, both six months prior to CMS-2728 submission and at the time of submission. Fourth, the catalog lists specified comorbid conditions, present either at the time of CMS-2728 submission or during the preceding ten years. Fifth, the catalog includes fields about health care utilization preceding initiation of renal replacement therapy. Sixth, the catalog includes biochemical measurements within the 45 days prior to CMS-2728 submission.

Regarding comorbid conditions, the 1995 and 2005 revisions of CMS-2728 are modestly different. In the former revision, specified conditions include congestive heart failure (CHF), ischemic heart disease, myocardial infarction, cardiac arrest, cardiac dysrhythmia, pericarditis, cerebrovascular disease (*i.e.*, cerebrovascular accident or transient ischemic attack), peripheral vascular disease (PVD), (history of) hypertension, diabetes (as either the primary cause of renal failure or a contributing factor), diabetes with current insulin treatment, chronic obstructive pulmonary disease (COPD), tobacco use, malignant neoplasm or cancer, alcohol dependence, drug dependence, human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), inability to ambulate, and inability to transfer. In the latter revision, specified conditions include CHF, atherosclerotic heart disease, other cardiac disease, cerebrovascular disease, PVD, (history of) hypertension, amputation, diabetes with current insulin treatment, diabetes

with current oral pharmacological treatment, diabetes without current pharmacological treatment, diabetic retinopathy, COPD, tobacco use, malignant neoplasm or cancer, toxic nephropathy, alcohol dependence, drug dependence, inability to ambulate, inability to transfer, need for assistance with daily activities, institutional residency, and non-renal congenital abnormality. Definitions of only ischemic heart disease, cerebrovascular disease, PVD, and drug dependence are delineated in some detail in the instructions for completion of CMS-2728. In fact, only one study has assessed the accuracy of comorbid conditions specified on CMS-2728. Longenecker *et al* estimated sensitivity and specificity of the 1995 revision to measure comorbidity in a sample of 1005 incident dialysis patients in the CHOICE (Choices for Healthy Outcomes in Caring for ESRD) study, with medical record documentation as the *de facto* gold standard measurement.[28] Sensitivity estimated ranged from a minimum of 0.15 to a maximum of 0.83. Among the most highly prevalent conditions, sensitivity estimates were 0.77 (95% confidence interval [CI], 0.75-0.80) for (history of) hypertension, 0.75 (0.71-0.79) for diabetes, 0.52 (0.47-0.56) for CHF, 0.48 (0.43-0.53) for ischemic heart disease, 0.15 (0.11-0.20) for cardiac dysrhythmia, and 0.40 (0.34-0.46) for PVD. The sensitivity of CMS-2728 to detect any cardiovascular disease was 0.61 (0.57-0.65). In contrast to sensitivity, specificity was generally high, with a range from 0.95 to 1.00.

Regarding health care utilization preceding initiation of renal replacement therapy, the 1995 revision merely provides data about pre-ESRD use of exogenous erythropoietin (EPO) for the treatment of anemia. The 2005 revision also provides data about use of EPO prior to ESRD. In addition, the 2005 revision indicates whether the patient received care from a nephrologist or a renal dietitian. The 2005 revision also

indicates the type of vascular access (arteriovenous fistula, graft, catheter, or other) in use during the first outpatient dialysis treatment.

Finally, regarding biochemical measurements, the 1995 and 2005 revisions both include values of serum albumin, serum creatinine, and either hematocrit or hemoglobin. Both revisions also include values of the lower limit of the normal range for serum albumin (*i.e.*, 3.5 g/dl for the bromcresol green dye-binding technique and 3.2 g/dL for the bromcresol purple technique), but these values are frequently missing. The 1995 revision also lists values of blood urea nitrogen (BUN), creatinine clearance, and urea clearance. The 2005 revision lists values of glycosylated hemoglobin (HbA1c) and serum lipids (total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides).

Payor History

The payor history is a sequential profile of payors of health care services for each ESRD patient, beginning with the initiation of renal replacement therapy. Each record in the history file represents a discrete time interval with a single level of payor categorization. The record includes beginning and ending dates for the interval. Levels of payor categorizations include Medicare as primary payor, with Parts A and B insurance; Medicare as primary payor, without both Parts A and B insurance; Medicare as secondary payor, in coordination with an employer group health plan (EGHP); Medicare as secondary payor, in coordination with a non-EGHP entity; Medicare health maintenance organization payor; non-Medicare payor; and unknown payor. Payor status is unknown during the first three calendar months of in-center hemodialysis treatment in patients without existing Medicare insurance at the time of initiation of renal replacement therapy.

In these patients, Medicare eligibility does not begin until the first day of the fourth calendar month of in-center hemodialysis treatment. The primary epidemiologic purpose of the payor history is identification of patients with Medicare as primary payor, with Parts A and B insurance. In these patients, the USRDS database includes all records of health care utilization billed to Parts A and B, including hospitalization, dialysis treatments, and physician services.

Residence History

The residence history is a sequential profile of the places of residence for each ESRD patient, beginning with the initiation of renal replacement therapy. Each record in the history file represents a discrete time interval with a single ZIP code as the most granular description of the place of residence. The record includes beginning and ending dates for the interval. The history file, by derivation from ZIP code, also includes identification of the county, state, and ESRD Network Organization of place of residence.

Treatment Modality History

The treatment modality history is a sequential profile of renal replacement therapies for each ESRD patient, beginning with the initiation of renal replacement therapy. Each record in the history file represents a discrete time interval with a single treatment modality (with an exception that I describe later). The record includes beginning and ending dates for the interval. Treatment modalities include hemodialysis, peritoneal dialysis (of unknown type), continuous ambulatory peritoneal dialysis, continuous circulatory peritoneal dialysis, dialysis (of unknown type), kidney transplant, recovery of endogenous renal function, and unknown modality. (ESRD is typically accompanied by a permanent need for renal replacement therapy, but a minority of

patients with reversible causes of renal failure may eventually discontinue therapy. Examples of such causes include allergic interstitial nephritis, athero-embolic renal disease, hemolytic-uremic syndrome, malignant hypertension, and scleroderma.) The USRDS also constructs a more detailed version of the treatment modality history, in which each of the aforementioned records is divided into discrete intervals accompanied by a single renal replacement therapy provider. Providers are identified by a numeric code, which can be used to aggregate patients receiving treatment at a dialysis facility, in a dialysis organization, or at a transplant program.

Medicare Part A Claims

Medicare Part A is commonly known as "hospital insurance." The USRDS database includes final action (*i.e.*, paid) Medicare Part A claims from 1991 to 2012 for all ESRD patients; these claims are extracted from CMS's Standard Analysis Files. The compendium of Part A claims is divided into four discrete subsets, according to the type of facility from which the claim originated. These subsets include hospice facilities, home health agencies, inpatient hospitals, and skilled nursing facilities; claims from inpatient hospital stays are most numerous. Medicare Part A claims are submitted via form CMS-1450 (also known as form UB-04). The key elements of CMS-1450 include the beginning and ending dates of service (*i.e.*, admission and discharge dates, in the case of hospital stays), value codes, diagnosis codes, E-codes, and procedure codes.

Value codes are primarily used to report financial data, but may be used to report clinical data, insofar as such data are deemed necessary to justify claims for particular health care services. In the context of Medicare Part A claims, an important use of value coding is to report the total number of pints of whole blood or units of packed red blood

cells that are furnished to a patient during the service interval. CMS-1450 may include up to twelve value codes. Diagnosis codes are reported in ICD-9-CM format. Each claim includes one principal diagnosis that is chiefly responsible for the health care encounter, along with a maximum of eight other diagnoses that either coexisted at the beginning of the encounter or developed subsequently. E-codes are also reported in ICD-9-CM format. These codes are used for supplementary classification of external causes of injury and poisoning. CMS-1450 may include one E-code. Finally, procedure codes are likewise reported in ICD-9-CM format. Among Part A claims, these codes are used primarily to report services during hospitalization. CMS-1450 may include a principal procedure code, along with a maximum of five other procedures. Per CMS regulations, the principal procedure must be performed for definitive treatment, rather than for diagnostic or exploratory purposes. Because of the structure of CMS-1450, procedures codes are not explicitly linked to diagnosis codes.

Beginning in October of 1983, Part A claims that originated from inpatient hospitals were reimbursed through a prospective payment system (PPS); Congress initiated this reform in an attempt to slow the escalation of Medicare costs during the preceding 15 years. Essentially, the PPS reimburses inpatient hospital facilities at a fixed rate per patient discharge, where the rate is a function of the diagnosis-related group (DRG) that is assigned to the hospitalization ending in that discharge. The majority of DRG assignments are decided by an automated algorithm (*i.e.*, with "grouper" software), although some are adjudicated during a formal review process. The DRG is determined from the principal diagnosis, secondary diagnoses specifying comorbid conditions present on admission or complications arising during hospitalization, any surgical

procedures performed during hospitalization, discharge status, age, and sex. In short, the DRG represents an alternative instrument for the identification of disease from Part A inpatient hospital claims. Beginning in July of 1998, Part A claims that originated from skilled nursing facilities were also reimbursed through a PPS, although the collection of applicable DRGs is different than the corresponding set of DRGs for inpatient hospital claims. In general, because the PPS serves as a substitute for itemized billing of rendered health care services, medication use in hospitals and skilled nursing facilities is not identifiable from Medicare claims.

Medicare Part B claims

Medicare Part B is commonly known as "supplemental medical insurance." Unlike Part A, which requires no premium payment from individuals who have accumulated at least forty quarters of employment (or whose spouse has accumulated at least forty quarters), Part B does require a monthly premium payment. Consequently, while entitlement for Medicare Parts A and B necessarily occurs simultaneously, enrollment in each part may not occur simultaneously. The USRDS database includes all final action Part B claims from 1991 to 2012 for ESRD patients; these claims are extracted from CMS's Standard Analysis Files. The compendium of Part B claims is divided into three discrete subsets, according to the type of health care institution or provider that submitted the claim. The subsets include outpatient facilities, carriers, and durable medical equipment (DME) suppliers. Claims from outpatient facilities are submitted via form CMS-1450, but claims from carriers and DME suppliers are submitted via form CMS-1500. CMS-1500 is considerably simpler in structure than CMS-1450, as CMS-1500 is designed only for itemized billing of health care procedures,

services, and supplies. In addition, unlike CMS-1450, the format of CMS-1500 allows explicit linkage of procedure codes with diagnosis codes.

Regarding outpatient facilities, these entities include outpatient hospital departments, rural health clinics, outpatient rehabilitation facilities, community mental health centers, and notably, dialysis facilities. (Therefore, while enrollment in Medicare Part B is generally elective, it is essentially mandatory in dialysis patients for whom Medicare is the primary payor.) Claims that originate from outpatient facilities include all of the elements that are included on Part A claims. Additionally, Part B claims that originate from outpatient facilities include itemized billing for medical services and supplies, including injectable medications. Each item is identified by a Healthcare Common Procedure Coding System (HCPCS) code. Codes may be specified in either HCPCS Level I or II format. HCPCS Level I codes, commonly known as Current Procedural Terminology (CPT) codes, are five-digit numeric codes that can be used to identify medical procedures and services. HCPCS Level II codes are five-character alphanumeric codes that can be used to identify durable medical equipment, (ordinarily non-oral) medications, orthotic and prosthetic procedures, and surgical supplies. Each item includes a date of service and, as applicable, the number of rendered units (*e.g.*, of a medication).

Part B claims that originate from carriers are mostly submitted by non-institutional health care providers, including physicians, physician assistants, nurse practitioners, and clinical social workers. Other examples of carriers include ambulance operators, (free-standing) ambulatory surgical centers, and independent clinical laboratories. Such claims include itemized billing for medical services and supplies. Each

item is identified by a HCPCS code and a corresponding ICD-9-CM diagnosis code that essentially justifies the item. Each item includes beginning and ending dates of service, and as applicable, the number of rendered units. Each item also includes the place of service, which is indicated by a two-digit numeric code that identifies the type of facility at which the item was rendered. Part B claims that originated from DME suppliers similarly include itemized billing for medical supplies.

Medicare Part D Enrollment Database

Medicare Part D is commonly known as "prescription drug insurance." Medicare Part D was instituted in 2006. Like Part B, enrollment in Part D requires a monthly premium, at least in the absence of documented poverty. In fact, Medicare enrollees who choose to forgo Part D coverage without possession of creditable (*i.e.*, at least actuarially equivalent) prescription drug insurance are penalized with higher monthly premiums upon eventual enrollment in Part D. The USRDS database includes Part D enrollment information from 2006 to 2011 for all ESRD patients with at least one month of enrollment in Medicare Parts A, B, or C (*i.e.*, Medicare Advantage) during a calendar year. (Patients not enrolled in Medicare Parts A, B, or C during a calendar year cannot enroll in Medicare Part D, so such patients are excluded by convention from the enrollment database.) For each patient, the database includes monthly data regarding Part D enrollment and dual eligibility (for Medicare and Medicaid) status. Additionally, the database includes an indication of whether the patient possessed creditable coverage from any of five sources for at least one month during the calendar year; these sources include the Federal Employees Health Benefits (FEHB) program, the TRICARE (formerly CHAMPUS) program, the Veterans Affairs (VA) program, any state pharmacy assistance

program (SPAP), or any employer group health plan. Creditable coverage admits the possibility that prescription medications may be obtained outside of Part D.

Specifically, for each calendar month in which a patient is enrolled in Medicare Parts A or B, the enrollment database indicates the source of prescription drug insurance: Part D with assistance via the low-income subsidy (LIS), Part D without assistance via the LIS, an employer group health plan reimbursed by CMS via the retiree drug subsidy (RDS), creditable coverage not through an employer group health plan, or no (known) prescription drug insurance. The LIS is designed to improve access to medications by subsidizing monthly premiums and reducing coinsurance for those individuals with limited financial resources. Individuals may be either deemed eligible for receipt of the LIS exclusively because of dual eligibility for Medicare and Medicaid or declared eligible for receipt of the LIS because of application to the Social Security Administration with documentation of both limited income and assets. For individuals who are deemed eligible, there are three degrees of assistance: no monthly premiums and no prescription copayments, no premiums and low copayments, and no premiums and high copayments. On the other hand, for individuals who are declared eligible, there are five degrees of assistance: no monthly premiums and high copayments, no premiums and 15% coinsurance, a 75% discount in premiums and 15% coinsurance, a 50% discount in premiums and 15% coinsurance, and a 25% discount in premiums and 15% coinsurance. Low copayments were set at maxima of $1.00, $1.00, $1.05, $1.10, $1.10, and $1.10 for generic medications in 2006, 2007, 2008, 2009, 2010, and 2011, respectively; for branded medications, corresponding copayments were set at maxima of $3.00, $3.10, $3.10, $3.20, $3.30, and $3.30. Alternatively, high copayments were set at maxima of $2.00,

$2.15, $2.25, $2.40, $2.50, and $2.50 for generic medications in 2006, 2007, 2008, 2009, 2010, and 2011, respectively; for branded medications, corresponding copayments were set at maxima of $5.00, $5.35, $5.60, $6.00, $6.30, and $6.30.

The RDS is essentially a tax-exempt rebate equal to 28% of qualifying medication costs incurred by retirees who possess prescription drug insurance through an employer group health plan; the rebate itself is payable to the employer. The RDS has progressively lost popularity since the advent of Part D, because its administrative simplicity actually betrays its relative cost inefficiency, compared to other options for providing prescription drug insurance to retirees.

For calendar months in which a patient is enrolled in Medicare Part D, the enrollment database specifies the selected contract, plan, and segment. The contract field represents the private entity (*e.g.*, CVS Caremark) that administers one or more Part D plans that have been approved by CMS. The first character of the field identifies the type of contract administrator: 'E' for employers; 'H' for managed care organizations (MCOs), excluding regional preferred provider organizations (PPOs); 'R' for regional PPOs; and 'S' for standalone administrators. Employer administration of Part D contracts is rare, and has been historically confined to labor unions. Both MCOs and regional PPOs administer Part D contracts as part of Medicare Part C (*i.e.*, Medicare Advantage), and therefore offer prescription drug insurance only in tandem with hospital and supplemental medical insurance. Standalone administrators offer prescription drug insurance without other forms of health insurance. Each contract may include multiple plans, which may vary in benefit structure and formulary constitution. Each plan may possess multiple segments, which cover mutually exclusive geographical regions.

Medicare Part D Events

In Part D, each prescription fill generates an event record (*i.e.*, a claim). The USRDS database includes all Part D events from 2006 to 2011 for ESRD patients. Each event record includes the National Drug Code (NDC) of the dispensed prescription. In data that are distributed by CMS, the NDC is an 11-digit numeric code with three segments: the first through fifth digits specify the labeler (*e.g.*, manufacturer), the sixth through ninth digits specify the product (*i.e.*, a specific agent, form, and strength), and the tenth and eleventh digits specify the package (*e.g.*, the tablet count). In the past, labelers were allowed to recycle previously assigned NDCs. Each record includes a date of service (*i.e.*, the date on which the prescription was filled), the quantity of medication that was dispensed, and the number of days that were thereby supplied. Each record also includes numeric codes that uniquely identify the medication prescriber and dispensing pharmacy.

Finally, each record specifies the benefit phase in which the prescription was filled. Each Part D plan has a unique benefit structure, but all plans must be at least actuarially equivalent to the standard benefit that is defined by CMS. In the standard benefit, there are four phases: the deductible phase, the pre-initial coverage limit (pre-ICL) phase, the initial coverage limit (ICL) phase, and the catastrophic phase. These phases are defined with respect to the calendar year; in other words, on January 1 of each year, all Part D enrollees begin in the deductible phase. In the deductible phase, an enrollee is responsible for all medication costs. In the pre-ICL phase, an enrollee is responsible for 25% of costs. Again in the ICL phase, an enrollee is responsible for all costs. Finally, in the catastrophic phase, an enrollee is responsible for only 5% of costs.

The boundaries between these phases are a function of cumulative medication costs, and are annually set by CMS. In 2006, 2007, 2008, 2009, 2010, and 2011, the deductible phase ended at $250, $265, $275, $295, $310, and $310 of cumulative costs, respectively. The pre-ICL phase ended at $2,250, $2,400, $2,510, $2,700, $2,830, and $2,840 of cumulative costs in corresponding years, while the ICL phase ended at $3,600, $3,850, $4,050, $4,350, $4,550, and $4,550 of cumulative out-of-pocket (OOP) costs. Enrollees may select plans that eliminate the deductible phase or provide coverage during the ICL phase (typically in exchange for higher monthly premiums). Importantly, the standard benefit is applicable only to patients who are not eligible for receipt of the LIS. For enrollees who are dually eligible and for enrollees who are not dually eligible, but who pay no monthly premiums and high copayments, there is no deductible phase, no distinction between pre-ICL and ICL phases (*i.e.*, copayments remain the same), and no out-of-pocket (OOP) cost in the catastrophic phase. For enrollees who are not dually eligible and pay 15% coinsurance, there is a small deductible phase, no distinction between the pre-ICL and ICL phases (*i.e.*, coinsurance remains the same), and high copayments in the catastrophic phase.

First DataBank™ Drug Database

Attached to each Part D event record in the USRDS database is drug information for the specified NDC, as listed in the First DataBank™ drug database. Such information is appended by CMS. Data includes the branded and generic names of the medication, both in text string format; the strength of the medication, in applicable units (*e.g.*, milligrams, micrograms, or percentage concentration); and the dosage form (*e.g.*, tablet,

capsule, or vial). Specifically, dosage form is listed with a two-character code that facilitates precise identification of route of administration.

Medi-Span™ Drug Database

In the Medi-Span drug database, each NDC is linked to a generic product identifier (GPI) code, which is a fourteen-character numeric identifier. Multiple NDCs may be mapped to a single GPI code. The format of the GPI code facilitates precise identification of both drug class and generic ingredient. Specifically, the first pair of digits indicates drug group (*e.g.*, diuretics); the second pair indicates drug class (*e.g.*, loop diuretics); the third pair indicates drug sub-class; the fourth pair indicates drug name; the fifth pair indicates drug name extension; and the sixth and seventh pairs indicates form and strength (although not in a systematic manner across all drugs).

Completeness of the USRDS Database

The primary instrument for the identification of a new ESRD patient is form CMS-2728 ("End Stage Renal Disease Medical Evidence Report; Medicare Entitlement and/or Patient Registration"). The form is used to establish Medicare eligibility for individuals who are not existing Medicare enrollees; to reclassify existing Medicare enrollees as ESRD patients; and to collect information about the demographic characteristics, comorbid diagnoses, biochemical measurements, and initial treatment modality of ESRD patients. Since April 1, 1995, providers have been required to submit CMS-2728 for all ESRD patients within 45 days of the initiation of renal replacement therapy (*i.e.*, dialysis or kidney transplant), regardless of considerations of either current or future need for Medicare insurance. Secondary instruments for the identification of a new ESRD patient include a Medicare Part A claim for a kidney transplant, a Medicare

Part B claim for dialysis treatment, or a kidney transplant recipient registration in the OPTN database. Given the statutory requirement for submission of form CMS-2728 and the breadth of secondary instruments listed here, the USRDS database is considered to be complete in its identification of patients who have initiated treatment for ESRD since April 1, 1995.

Chapter 3

Risk Scores Developed from Prescription Drug Claims in Dialysis Patients

Abstract

Risk scores can be useful in both clinical and epidemiologic applications. Many scores are functions of diagnosed diseases; fewer are functions of dispensed medications. In chronic dialysis patients, in whom polypharmacy is common, scores based on medication, rather than disease, may be superior metrics of prognosis. We used Medicare Part D data to construct 4 risk scores for dialysis patients. Separately in incident and prevalent (*i.e.*, undergoing dialysis for ≥ 1 year) patients, we constructed scores for each of death and hospitalization. In incident patients, medications were ascertained from Part D claims during the 1 year preceding dialysis initiation, whereas in prevalent patients, medications were ascertained from claims during a calendar year. Scores were constructed with a pre-specified algorithm that used training, validation, and testing sets from 2008, 2009, and 2010, respectively. In the testing set, we compared the performance of risk scores based on medications versus scores based on diseases (Deyo, van Walraven, and Liu) versus both. For incident patients, risk scores for death and hospitalization included 19 and 15 components, respectively, whereas for prevalent patients, corresponding scores included 28 and 20 components. Cardiovascular agents were the most common constituents of each score. Each score was monotonically associated with crude rates of death and hospitalization in the testing set. For each pair of cohort and event, explained variation for the score based on medication was less than explained variation for one or more scores based on disease. However, the explained variation associated with simultaneous use of two scores, one based on medication and

another based on disease, was always greater than explained variation associated with one score. In conclusion, risk scores as functions of prescription drug claims in dialysis patients are useful metrics for summarizing future risk of death and hospitalization. In epidemiologic applications, simultaneous use of scores based on comorbid disease and dispensed medication is probably preferable to use of a score based on only one domain.

Introduction

According to the most recent census by the United States Renal Data System (USRDS), there were more than 450,000 chronic dialysis patients alive in the US at the end of 2012.[29] Rates of death and hospitalization among dialysis patients remain much higher than corresponding rates in the US population.[30] Thus, there is an ongoing need to identify medical interventions that can reduce the incidence of mortality and morbidity in dialysis patients. Pharmacologic therapy is a key dimension of intervention for all chronic diseases, but its application to dialysis patients is often complicated by the lack of rigorous evidence demonstrating efficacy and safety in patients with advanced chronic kidney disease. Specifically, patients with either elevated serum creatinine or end stage renal disease (ESRD) are typically excluded from randomized clinical trials of new medications.[31] This gap in evidence creates a pressing need for observational studies. Fortuitously, dialysis patients are an excellent target for observational studies, including retrospective cohort studies, because of the availability of several large datasets.[32] Roughly two in three dialysis patients receive care from one of two dialysis provider organizations and the electronic health records of each organization allow analysis of more than 150,000 contemporary patients.[29] All patients that initiate chronic dialysis are eligible for Medicare Part A (*i.e.*, hospital insurance) and Part B (*i.e.*, medical insurance) upon the first day of the fourth calendar month of treatment, regardless of age or disability status. Moreover, many dialysis patients are poor and concurrently enrolled in both Medicare and Medicaid, thereby resulting in automatic enrollment in Medicare Part D (*i.e.*, prescription drug coverage). Medicare Parts A and B claims allow analysis of more than 300,000 contemporary patients and Part D claims allow further analysis in a

subset of more than 200,000 patients. For example, Part D claims were recently analyzed to assess the comparative effectiveness of sevelamer (carbonate or hydrochloride) versus calcium acetate in hemodialysis patients.[33]

An important challenge with observational studies of medical interventions is the threat posed by confounding, which manifests when patients that receive an intervention differ in baseline risk from those who do not receive the intervention.[34] Statistical adjustment for factors that correlate with receipt of an intervention may address confounding. In the case of dialysis patients, adjustment for comorbidity burden is a requisite element of study design, due to the relatively high prevalence of heart failure, atherosclerotic heart disease, diabetes, chronic obstructive pulmonary disease, and mineral metabolism disorders. Comorbidity scoring is a popular technique that quantifies comorbidity burden. The Charlson Comorbidity Index is a frequently used score that includes 16 conditions; each condition is tagged with a number of points and the points of all diagnosed diseases are summed to characterize risk of death.[35] Many other indices have been developed.[36] However, whether comorbidity scoring can be developed in one population and applied in another population is generally unclear, as comorbid conditions may heterogeneously associate with risk in disparate settings. To that point, several indices have been recently developed in dialysis patients.[37-39] However, all of the indices for dialysis patients have been based on diagnoses of comorbidity. None have been based on receipt or use of medication. Dialysis patients take 11 medications (on average).[40] Prescription medication likely reflects comorbidity burden and data about receipt of medications may be more accurate than data about comorbidity, particularly when data

are ascertained from Medicare claims. In principle, comorbidity scoring as a function of dispensed medications may be a useful tool for observational studies.

In this study, we used USRDS data to create for dialysis patients a series of comorbidity scores as functions of dispensed medications; data about medication were ascertained from Part D claims. In cohorts of incident and prevalent dialysis patients, we created scores that associate with risks of death and hospitalization. We analyzed consecutive annual cohorts of patients to develop, test, and validate scores. Finally, we compared the performance of the proposed scores with three published scores based on diagnoses ascertained from Parts A and B claims.

Methods

We analyzed USRDS data that were obtained through a Data Use Agreement with the National Institute of Diabetes and Digestive and Kidney Diseases. We identified cohorts of incident and prevalent patients; in each case, we identified cohorts in 2008 (training set), 2009 (validation set), and 2010 (testing set). For the incident cohort in year *Y*, we retained patients with date of initiation of chronic hemodialysis (*i.e.*, index date) between January 1 and December 31 of year *Y*; age greater than or equal to 66 years on the index date; uninterrupted enrollment in Medicare Part D during the 12-month interval immediately preceding the index date (*i.e.*, entry interval); and non-missing data regarding race, Hispanic ethnicity, primary cause of ESRD, and ESRD Network of residence on the index date. For the prevalent cohort in year *Y*, we retained patients with receipt of chronic dialysis on December 31 of year *Y* (*i.e.*, index date), uninterrupted receipt of one dialytic modality (*i.e.*, either hemodialysis or peritoneal dialysis) during

year *Y*, and date of initiation of renal replacement therapy no later than October 31 of year $Y - 1$; age greater than or equal to 20 years on the index date; uninterrupted enrollment in Medicare Part D during the 12-month interval immediately preceding the index date (*i.e.*, entry interval); and non-missing data regarding race, ethnicity, primary cause of ESRD, and ESRD Network of residence. For development of scores associated with risk of hospitalization, we limited cohorts to patients with uninterrupted enrollment in Medicare Parts A and B during the entry interval.

For each patient, we identified age on the index date, race (white, black, Asian, Native American, other race), sex, primary cause of ESRD (diabetes, hypertension, glomerulonephritis, polycystic kidney disease, other known cause, unknown cause), and ESRD Network of residence on the index date. We refer to these characteristics as demographic factors.

For development of scores associated with risk of mortality, follow-up began on the index date and ended on the earliest of the date of death, the date of kidney transplant, or the date that was one year after the index date. The target event was time to death. Scores were developed with Cox proportional hazards regression, with simultaneous adjustment for demographic factors. For development of scores associated with risk of hospitalization, follow-up was identical, except that follow-up also ended at interruption of enrollment in Parts A and B. The target event was cumulative hospitalized days in the follow-up interval, with days ascertained from Part A claims for inpatient facility care. Scores were developed with Poisson regression, with an offset for follow-up time and simultaneous adjustment for demographic factors. In all regressions, age was parameterized with a cubic polynomial (for flexibility).

Receipt of medication was ascertained from Part D claims during the 12-month interval immediately preceding the index date. For dialysis patients that were enrolled in each of Parts A, B, and D, Part D claims comprised medications that were administered in the home, as those that were intravenously administered during dialysis (*e.g.*, erythropoiesis-stimulating agents, iron, and vitamin D sterols) were covered by Part B. We examined the National Drug Code (NDC) of each dispensed medication and mapped the NDC to a Generic Product Identifier (GPI) in the Medi-Span Master Drug Database (Indianapolis, IN). The GPI taxonomy categorizes each medication according to a hierarchy of group, class, subclass, active moiety, and salt. Separately for incident and prevalent cohorts, we queried Part D claims in the training and validation sets to identify subclasses with prevalence of use (*i.e.,* at least one dispensed medication) greater than or equal to 0.5% in both sets. Only those subclasses with such level of prevalence were considered for inclusion in scores.

For each combination of cohort and event, we applied the following algorithm:

(1) In the training set, we sequentially added subclasses to the event model on the basis of maximal incremental change in explained variation (EV), until the change in EV was less than 0.1% with the addition of any outstanding subclass; by convention, the EV of the model with only demographic factors was equal to 0%. In detail, we identified first the subclass associated with maximal EV; we identified second the subclass associated with maximal change in EV, conditional upon inclusion of the first subclass; and so on. For Cox and Poisson regressions, EV was estimated by R^2 metrics based on partial likelihood statistics and deviance

residuals, respectively.[41-42] From each fitted model in the sequence, we retained the estimates of parameters associated with subclasses.

(2) In the validation set, we fit each model in the sequence identified in (1). The parameters associated with demographic factors were re-estimated from data in the validation set, but the parameters associated with subclasses were fixed at the values identified in (1). We identified models with incremental change in EV less than 0.05% and eliminated from further development the subclasses that distinguished each such model from its respective antecedent in the sequence.

(3) In the training set, we refit the event model with subclasses that were retained in (2). For each instance of multiple subclasses within the same class, we also refit the event model with joined subclasses. From each refitted model, we retained the estimates of parameters associated with subclasses and joined subclasses.

(4) In the validation set, we refit each of the models in (3). The parameters associated with demographic factors were re-estimated from data in the validation set, but the parameters associated with subclasses and joined subclasses were fixed at the values identified in (3). For each model with joined subclasses, we calculated the difference between the EV of that model and the EV of the model without joined subclasses. We joined subclasses in further development if the difference was greater than -0.05%.

(5) We inspected the set of subclasses and joined subclasses that were identified in (4) and made minor revisions to the set to harmonize definitions across combinations of cohort and event and to improve relevance in dialysis patients.

All revisions are displayed in Appendix 1. We refer to the revised set of subclasses and joined subclasses as medication factors.

(6) In the validation set, we refit the event model with medication factors that were identified in (5). We assigned to each medication factor an integer number of points, according to the following function of the corresponding estimated parameter:

$$f(\beta) = \mathrm{sgn}(\beta) \times \left\{ 1 + \left\lfloor \frac{\max(0.025, |\beta|) - 0.025}{0.05} \right\rfloor \right\}$$

For each patient, the comorbidity score was finally derived as the sum of points associated with medication factors with at least one dispensed medication.

In the testing set, we assessed the characteristics of each comorbidity score. We estimated the distribution of each score and associations of each score with absolute risk. In testing set patients with concurrent enrollment in Medicare Parts A, B, and D during the entry interval, we also compared the performance of each comorbidity score with the performance of 3 scores that are functions of diagnosed diseases: the Deyo adaptation of the Charlson comorbidity index;[43] the van Walraven adaptation of the Elixhauser comorbidity index;[44] and the Liu comorbidity index, which was developed in dialysis patients.[38] Each comorbid condition was ascertained from Parts A and B claims during the entry interval. We declared a condition to be present if we identified at least one inpatient facility, skilled nursing facility, or home health agency claim or at least two outpatient facility or physician claims with qualifying *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes.[45] We compared EV associated with each score by nonparametric bootstrapping with 2000

samples; EV was estimated from a model that included demographic factors. Finally, we assessed whether EV associated with pairs of scores was greater than EV associated with individual scores.

All analyses were conducted in SAS, version 9.2 (Cary, North Carolina).

Results

For the incident cohort, we identified 27,075, 28,504, and 29,245 patients in the training, validation, and testing sets, respectively. Nearly 90% of patients in each set were between ages 65 and 84 years, more than 70% were white, and slightly more than 50% were female (Table 3-1). Diabetes and hypertension were the primary causes of ESRD for almost 80% of patients. More than 55% of patients were enrolled in Medicare Parts A and B. For the prevalent cohort, we identified 163,336, 171,381, and 181,340 patients in the training, validation, and testing sets, respectively. The majority of patients in each set were between ages 20 and 64 years, more than 40% were black, and slightly more than 50% were male (Table 3-1). The proportion of patients with either glomerulonephritis or polycystic kidney disease as the primary cause of ESRD was larger than in the incident cohort. More than 80% were enrolled in Medicare Parts A and B.

Initially in score development, medication subclasses were sequentially added to an event model, according to maximization of EV in the training set. The results of this step are displayed in Figure 3-1. For the incident cohort, we identified 20 subclasses associated with death risk and 16 associated with hospitalization risk. With adjustment for demographic factors, 10.9% and 5.7% of variation in death and hospitalization risks, respectively, were accounted by these subclasses. For the prevalent cohort, we identified

32 subclasses associated with death risk and 20 associated with hospitalization risk. With adjustment for demographic factors, 14.0% and 8.5% of variation in death and hospitalization risks, respectively, were accounted by these subclasses.

For incident patients, the components of death and hospitalization scores are displayed in Tables 3-2 and 3-3, respectively. For death, component values ranged from –13 to +8. Among 19 components, 15 (79%) were used by ≥ 5% of testing set patients; for such components, values ranged from –6 to +6. Cardiovascular agents constituted 9 components and psychotropic agents constituted 3 components. The distribution of scores in the testing set is displayed in Figure 3-2A. The mean score was –3.2 (standard deviation, 8.9). For hospitalization, component values ranged from –20 to +8. Among 15 components, 12 (80%) were used by ≥ 5% of testing set patients; for such components, values ranged from –6 to +5. Cardiovascular agents constituted 3 components and 4 therapeutic groups each included 2 components. The distribution of scores in the testing set is displayed in Figure 3-2B. The mean score was –1.3 (standard deviation, 6.7).

For prevalent patients, the components of death and hospitalization scores are displayed in Tables 3-4 and 3-5, respectively. For death, component values ranged from –4 to +9. Among 28 components, 21 (75%) were used by ≥ 5% of testing set patients; for such components, values ranged from –4 to +8. Cardiovascular agents constituted 8 components and digestive agents constituted 4 components. The distribution of scores in the testing set is displayed in Figure 3-2C. The mean score was 7.5 (standard deviation, 8.9). For hospitalization, component values ranged from –3 to +7. Among 20 components, 18 (90%) were used by ≥ 5% of testing set patients; for such components, values ranged from –3 to +6. Cardiovascular agents constituted 5 components and

neurological agents constituted 4 components. The distribution of scores in the testing set is displayed in Figure 3-2D. The mean score was 11.1 (standard deviation, 8.3).

Percentiles of each score and rates of death and hospitalization in groups of percentiles are displayed in Table 3-6. For incident patients, percentile groups were monotonically associated with rates of death and hospitalization. Relative to rates in those with scores between percentiles 0 and 4, rates in those with scores between percentiles 95 and 99 were 7.6 times greater for death and 4.2 times greater for hospitalization. For prevalent patients, percentile groups were likewise monotonically associated with rates of death and hospitalization. The death rate in those with scores between percentiles 95 and 99 was 7.0 times greater than the rate in those with scores between percentiles 0 and 4; for hospitalization, the rate in those with scores between percentiles 95 and 99 was 6.7 times greater than the rate in those with scores between percentiles 0 and 9.

Comparisons of EV in the testing set with comorbidity scores as functions of diagnosed diseases, comorbidity scores as functions of dispensed medications, and combinations thereof are displayed in Figure 3-3; in these cases, EV included the contribution of demographic factors. For death in incident patients, EV associated with the medication score was 17.5%, slightly less than with the van Walraven (17.7%) disease score, but greater than with other disease scores (Figure 3-3A). EV associated with the combination of medication and van Walraven scores was 22.9%. For hospitalization, EV associated with the medication score was 10.2%, slightly less than with the van Walraven (10.9%) and Liu (10.7%) disease scores (Figure 3-3B). EV associated with the combination of medication and van Walraven scores was 14.4%. For

death in prevalent patients, EV associated with the medication score was 31.0%, less than with the van Walraven (31.9%) and Liu (33.8%) scores (Figure 3-3C). Highest was the combination of medication and Liu scores (37.7%). Finally, for hospitalization, EV associated with the medication score was 10.8%, lower than with the van Walraven (11.9%) and Liu (15.2%) scores (Figure 3-3D). Highest again was the combination of medication and Liu scores (17.0%).

Discussion

Risk scores are useful tools for clinical and epidemiologic research. In the clinical setting, risk scores can be used to set inclusion criteria of prospective studies, so that event rates might be accurately forecasted and sample size might be appropriately set to achieve statistical power. In epidemiologic studies, especially regarding comparative effectiveness, risk scores can be used to control confounding; the dimensionality reduction that is inherent in risk scores is useful in small cohorts and in studies of rare outcomes, such as hypersensitivity reactions. Ongoing need for epidemiologic studies in dialysis patients is pronounced, because nephrology publishes fewer randomized clinical trials per year than any other internal medicine specialty. Risk scores have traditionally been functions of diagnosed diseases, but this paradigm can be problematic for some sources of comorbidity data. When diagnosis codes are ascertained from administrative databases, in which sensitivity of codes may be low, risk scores themselves may be inaccurate metrics of prognosis; this information bias can engender residual confounding when scores are applied to risk adjustment schema. Alternatively, scores may be functions of prescription drug claims, which are *bona fide* evidence of dispensed

medications. However, drug claims implicitly conflate the effects of disease and the treatment thereof, thus resulting in unpredictable and possibly weak associations with risk.

In this study, we constructed and validated 4 risk scores as functions of drug claims in dialysis patients. Scores were constructed as proxies of death and hospitalization risks in the 1 year after dialysis initiation, as well as proxies of death and hospitalization risks in a calendar year, among patients with at least 1 year on dialysis. Risk scores included between 15 and 28 components and cardiovascular agent subclasses were important contributors to each score. Moreover, scores were monotonically associated with crude rates of death and hospitalization and rate ratios for highest versus lowest vigintiles of scores were between 4 and 8. However, in comparison to scores based on diagnosed diseases, scores based on drug claims were associated with slightly less explained variation in event incidence in a contemporary cohort. On the other hand, pairs of risk scores based on diseases and drug claims were associated with significantly more explained variation than single risk scores.

For incident patients, risk scores include several notable elements. First, regarding the score for death risk, three components – type III anti-arrhythmics, potassium-sparing diuretics, and potassium (supplements) – are related to the risk of cardiac dysrhythmia. Sudden cardiac death is the primary cause of death in 30% of cases during 1 month after dialysis initiation and in 25% of cases during 1 year after initiation.[46] Second, calcium channel blockers were tagged with −6 and −4 points for death and hospitalization scores, respectively. In the Dialysis Morbidity and Mortality Study Wave 2 cohort, which included 2,877 incident dialysis patients with ≥ 1 antihypertensive medication

prescription, both dihydropyridine and non-dihydropyridine calcium channel blockers were associated with significantly lower risk of death, after adjustment for pre-dialysis blood pressure, in contrast to all other subclasses of blood pressure-lowering medications.[47] Third, megestrol acetate was tagged with +8 points for the death score. Megestrol can be prescribed to stimulate appetite;[48] malnutrition is an important risk factor for death in new dialysis patients.[49] Fourth, both phosphate binders and oral vitamin D sterols were tagged with negative points for death and hospitalization scores. Treatment of mineral and bone disease is often initiated after dialysis initiation, but these point values suggest that initiation of treatment before beginning dialysis may lower risk of mortality and morbidity during the first year of dialysis. Fifth, several subclasses of psychotropic agents were tagged with positive points. Depression is associated with increased risk of death in dialysis patients.[50]

In prevalent patients, risk scores based on drug claims were associated with significantly less explained variation than the Liu score based on diagnosed diseases. The Liu index includes 11 diseases: atherosclerotic heart disease, cardiac dysrhythmia, congestive heart failure, other cardiac disease, cerebrovascular disease, peripheral vascular disease, cancer, chronic obstructive pulmonary disease, diabetes, gastrointestinal bleeding, and liver disease.[38] Atherosclerotic heart disease and diabetes are tagged with +1 point, congestive heart failure is tagged with +3 points, and all other diseases are tagged with +2 points. Ironically, the point values in the Liu index were derived from a Cox regression of death in incident dialysis patients in 2000, although follow-up of those patients did not begin until the end of the ninth month on dialysis and did not end until the end of 2005. The relatively better performance of the Liu index may be attributed to

the high volume of Parts A and B claims during the first year of dialysis; with a large number of claims, major comorbid conditions may be accurately identified.

This study has some limitations. First, data regarding both dispensed medications and hospitalization were ascertained from Medicare claims. Because Medicare Part D has a unique benefit structure, drugs claims are generated not only by medical need, but also by wherewithal to purchase medication. Application of these risk scores to dialysis patients with commercial insurance may be inappropriate. Second, risk scores were constructed with data from 2008 to 2010. Medicare Part D has evolved since 2010 and rates of both death and hospitalization have declined in dialysis patients.[29] Risk scores should be periodically evaluated for applicability in contemporary patients. As a concrete example, beginning in 2011, lidocaine/prilocaine was no longer covered by Part D in dialysis patients, as the item is typically used to prepare the vascular access and is therefore covered by Part B. Third, performance of risk scores based on diseases is predicated on ascertaining disease from ICD-9-CM diagnosis codes. However, Medicare will replace ICD-9-CM with ICD-10-CM later in 2015. This conversion may affect the accuracy of codes in claims and thereby reposition the relative performance of scores based on drug claims.

In conclusion, risk scores can be constructed from prescription drug claims in dialysis patients. The gradient of death and hospitalization rates across risk score distributions suggests that scores can be useful in both clinical and epidemiologic settings. Moreover, the components of the scores in this study (and their associated indications) may be fruitful targets for further research oriented toward improving clinical outcomes. As tools for risk adjustment schema, the scores in this study are

probably best used in tandem with previously published scores based on diagnosed diseases. Further research is needed to construct “hybrid” risk scores that combine diseases and drug claims into a single metric, as well as to construct risk scores that apply to dialysis patients without Medicare coverage.

Table 3-1. Characteristics of patients in incident and prevalent cohorts

	Incident cohort			Prevalent cohort		
	Training	Validation	Testing	Training	Validation	Testing
Sample size	27,075	28,504	29,245	163,336	171,381	181,340
Age (%)						
20-44 years				14.9	14.4	14.1
45-54 years				17.7	17.6	17.4
55-64 years				22.2	22.8	23.3
65-74 years	44.8	45.0	45.4	24.1	24.1	23.9
75-84 years	42.8	42.3	41.8	16.6	16.5	16.5
≥ 85 years	12.4	12.7	12.8	4.5	4.6	4.8
Race (%)						
White	70.7	70.3	70.8	50.3	50.8	51.1
Black	23.6	23.6	23.0	42.9	42.4	41.9
Native American	0.8	0.8	0.8	1.6	1.5	1.5
Asian	4.9	5.2	5.4	4.7	4.8	5.0
Other	< 0.1	< 0.1	< 0.1	0.6	0.5	0.4
Sex (%)						
Female	51.7	51.1	50.6	48.1	47.9	47.6
Male	48.3	48.9	49.4	51.9	52.1	52.4
Primary cause of ESRD (%)						
Diabetes mellitus	44.3	43.6	44.2	44.1	44.5	44.8
Hypertension	35.4	36.0	35.4	29.3	29.4	29.5
Glomerulonephritis	3.5	3.6	3.5	10.6	10.2	9.9
Polycystic kidney disease	0.8	0.8	0.8	2.4	2.4	2.4
Other known cause	12.0	12.2	12.6	10.2	10.1	10.2
Unknown cause	4.0	3.9	3.5	3.5	3.4	3.3
Parts A and B enrollment (%)	57.5	55.9	55.4	82.5	81.0	80.2

Abbreviation: ESRD, end stage renal disease.

Table 3-2. Components of risk score for death in incident patients

Subclass	GPI	Users [a] (%)	Points
Antimicrobial agents			
Fluoroquinolones	050000	35.9	+3
Cardiovascular agents			
Anti-arrhythmics (type III)	354000	6.5	+6
Calcium channel blockers	340000	64.8	–6
Digoxin	312000	7.1	+5
Nitrates	321000	28.0	+3
Peripheral alpha antagonists	362020	13.6	–3
Potassium-sparing diuretics	375000	8.5	+6
Statins	394000	62.7	–2
Vasodilators	364000	28.2	–4
Warfarin sodium	832000	16.6	+4
Dermal agents			
Lidocaine/prilocaine	9085990290	1.8	–13
Electrolytes			
Potassium	797000	23.4	+4
Hormonal agents			
Megestrol acetate	2140402010	4.2	+8
Mineral and bone disease agents			
Phosphate binders	528000	19.0	–5
Vitamin D sterols (oral)	309050	30.2	–6
Psychotropic agents			
Acetylcholinesterase inhibitors	620510	4.6	+5
Phenothiazines	592000	3.0	+5
Selective serotonin reuptake inhibitors	581600	17.5	+3
Respiratory agents			
Anticholinergics (inhaled)	441000, 442099	11.0	+4

Abbreviation: GPI, Generic Product Identifier.

[a] Among testing set patients.

Table 3-3. Components of risk score for hospitalization in incident patients

Subclass	GPI	Users [a] (%)	Points
Antimicrobial agents			
Antibiotics for *C. difficile*	1600003500, 1600006010	5.6	+3
Cardiovascular agents			
Calcium channel blockers	340000	64.0	–4
Thienopyridine derivatives	851580	21.6	+2
Warfarin sodium	832000	17.3	+5
Dermal agents			
Lidocaine/prilocaine	9085990290	1.9	–20
Topical enzymes	907000	1.8	+8
Digestive agents			
Lactulose	5240002000	5.1	+5
Proton pump inhibitors	528000	40.7	+2
Electrolytes			
Potassium	797000	24.2	+2
Mineral and bone disorder agents			
Phosphate binders	528000	18.9	–6
Vitamin D sterols (oral)	309050	29.1	–5
Neurological agents			
Hydantoins	722000	1.2	+6
Psychotropic agents			
Acetylcholinesterase inhibitors	620510	5.2	+5
Selective serotonin reuptake inhibitors	581600	19.0	+2
Respiratory			
Anticholinergics (inhaled)	441000, 442099	11.4	+3

Abbreviation: GPI, Generic Product Identifier.

[a] Among testing set patients concurrently enrolled in Parts A and B.

Table 3-4. Components of risk score for death in prevalent patients

Subclass	GPI	Users [a] (%)	Points
Antimicrobial agents			
Aminopenicillins	012000	13.9	–2
Antibiotics for *C. difficile*	1600003500, 1600006010	7.8	+3
Fluoroquinolones	050000	32.2	+3
Cardiovascular agents			
Alpha-beta blockers	333000	29.2	+3
Anti-arrhythmics (type III)	354000	5.0	+7
Calcium channel blockers	340000	53.3	–2
Digoxin	312000	3.5	+6
Midodrine hydrochloride	3800008310	5.1	+6
Nitrates	321000	17.8	+4
Statins	394000	47.1	–3
Warfarin sodium	832000	13.5	+4
Dermal agents			
Lidocaine/prilocaine	9085990290	16.4	–4
Silver sulfadiazine	9045003000	3.4	+5
Topical enzymes	907000	2.8	+9
Digestive agents			
Antiperistaltics	471000	6.9	+3
Metoclopramide	5230002010	12.0	+4
Polyethylene glycol 3350	4699200430, 4699200520, 4699200530, 4699200630	10.7	–2
Proton pump inhibitors	528000	43.9	+2
Hormonal agents			
Glucocorticosteroids	221000	15.4	+3
Megestrol acetate	2140402010	5.9	+8
Neurological agents			
Hydantoins or valproic acid	722000, 725000	4.0	+5
Hydrocodone with acetaminophen	659917	41.9	+3
Opioid agonists (without non-opioid analgesic)	651000	20.0	+5
Nutritional agents			
Amino acid infusion	803020	1.1	+8
Psychotropic agents			
Acetylcholinesterase inhibitors	620510	2.7	+5
Benzisoxazoles or butyrophenones	590700, 591000	2.2	+7
Selective serotonin reuptake inhibitors or tetracyclic antidepressants	580300, 581600	21.9	+4
Respiratory agents			
Anticholinergics (inhaled)	441000, 442099	7.6	+6

Abbreviation: GPI, Generic Product Identifier.

[a] Among testing set patients.

Table 3-5. Components of risk score for hospitalization in prevalent patients

Subclass	GPI	Users [a] (%)	Points
Antimicrobial agents			
Antibiotics for *C. difficile*	1600003500, 1600006010	8.0	+5
Fluoroquinolones	050000	32.7	+3
Cardiovascular agents			
Anti-arrhythmics (type III)	354000	5.0	+4
Central alpha agonists	362010	24.5	+3
Nitrates	321000	17.4	+3
Thienopyridine derivatives	851580	19.5	+3
Warfarin sodium	832000	13.4	+6
Dermal agents			
Lidocaine/prilocaine	9085990290	16.5	–3
Silver sulfadiazine	9045003000	3.4	+5
Digestive agents			
Metoclopramide	5230002010	12.5	+4
Proton pump inhibitors	528000	44.9	+3
Hormonal agents			
Glucocorticosteroids	221000	15.7	+3
Megestrol acetate	2140402010	6.0	+5
Neurological agents			
Gamma-aminobutyric acid analogues	7260003000, 7260005700	20.9	+3
Hydrocodone with acetaminophen	659917	43.0	+3
Oxycodone with acetaminophen	659900	18.7	+4
Opioid agonists (without non-opioid analgesic)	651000	20.8	+5
Psychotropic agents			
Dibenzothiazepines	591530	2.5	+7
Selective serotonin reuptake inhibitors	581600	20.4	+4
Respiratory agents			
Anticholinergics (inhaled)	441000, 442099	7.8	+6

Abbreviation: GPI, Generic Product Identifier.

[a] Among testing set patients concurrently enrolled in Parts A and B.

Table 3-6. Risk score percentiles and crude event rates, by risk percentile group

	Incident cohort		Prevalent cohort	
	Death	Hospitalization	Death	Hospitalization
Risk score percentile				
5	–17	–13	–4	0
10	–14	–9	–2	0
25	–9	–4	+1	+5
50	–3	0	+6	+10
75	+2	+3	+12	+16
90	+8	+7	+20	+23
95	+13	+9	+24	+27
Crude event rate,[a] by risk score percentile group				
0-4	14.5	11.7	7.5	4.4[b]
5-9	19.2	15.4	9.5	4.4[b]
10-24	23.1	18.1	10.3	6.5
25-49	30.8	24.9	13.1	9.4
50-74	43.9	29.8	19.0	12.9
75-89	60.6	36.5	28.3	17.8
90-94	77.9	39.7	37.3	23.4
95-99	110.3	48.8	52.5	29.6

Abbreviation: NA, not applicable.

[a] Deaths per 100 patient-years or hospitalized days per patient-year.

[b] The percentile groups of 0-4 and 5-9 constitute one group, which comprises patients with risk scores of –3 or 0.

Figure 3-1. Explained variation with sequential addition of medication subclasses to event model in training set

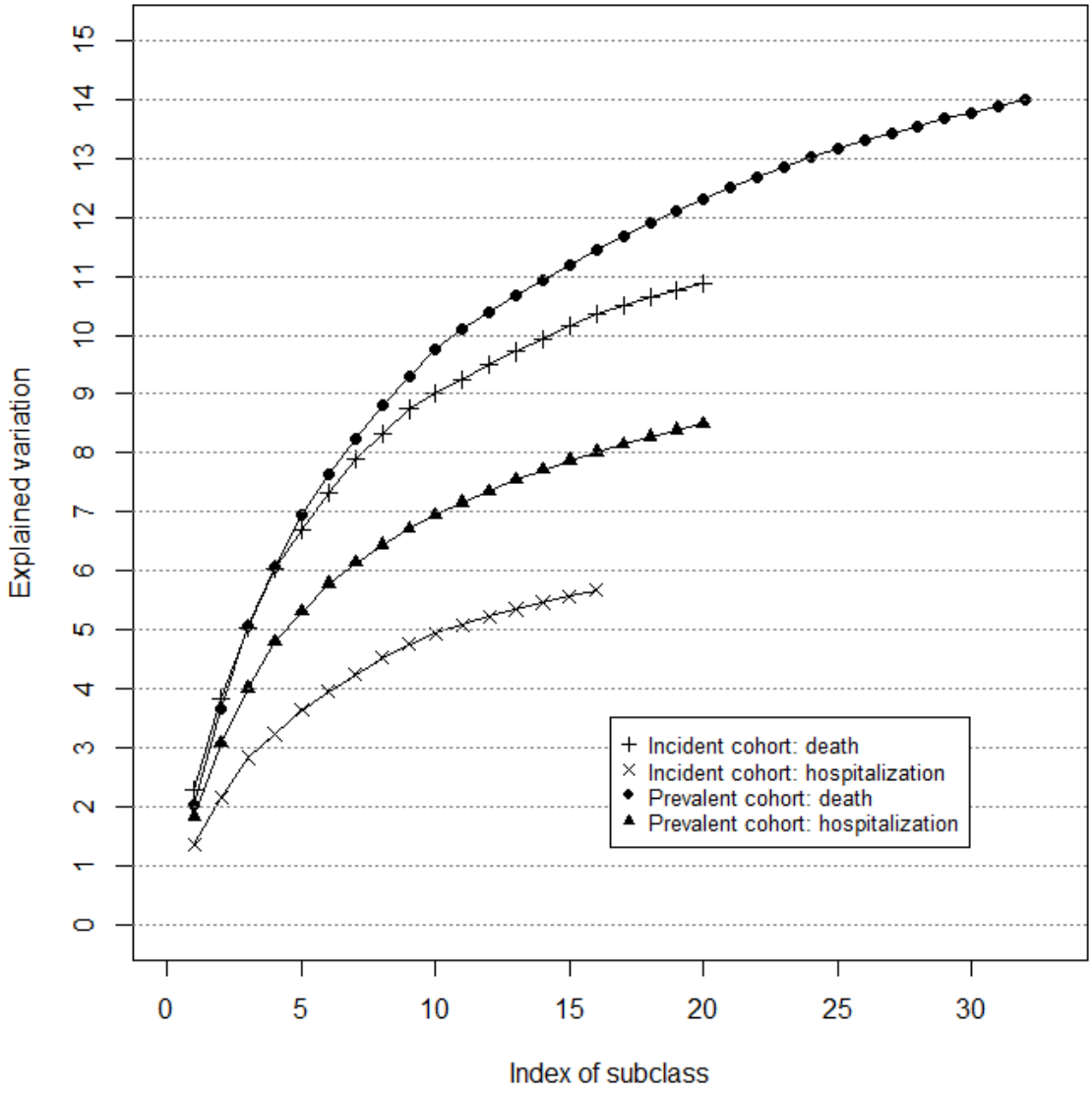


Figure 3-2A. Risk score distribution in the testing set, for the event of death in incident patients

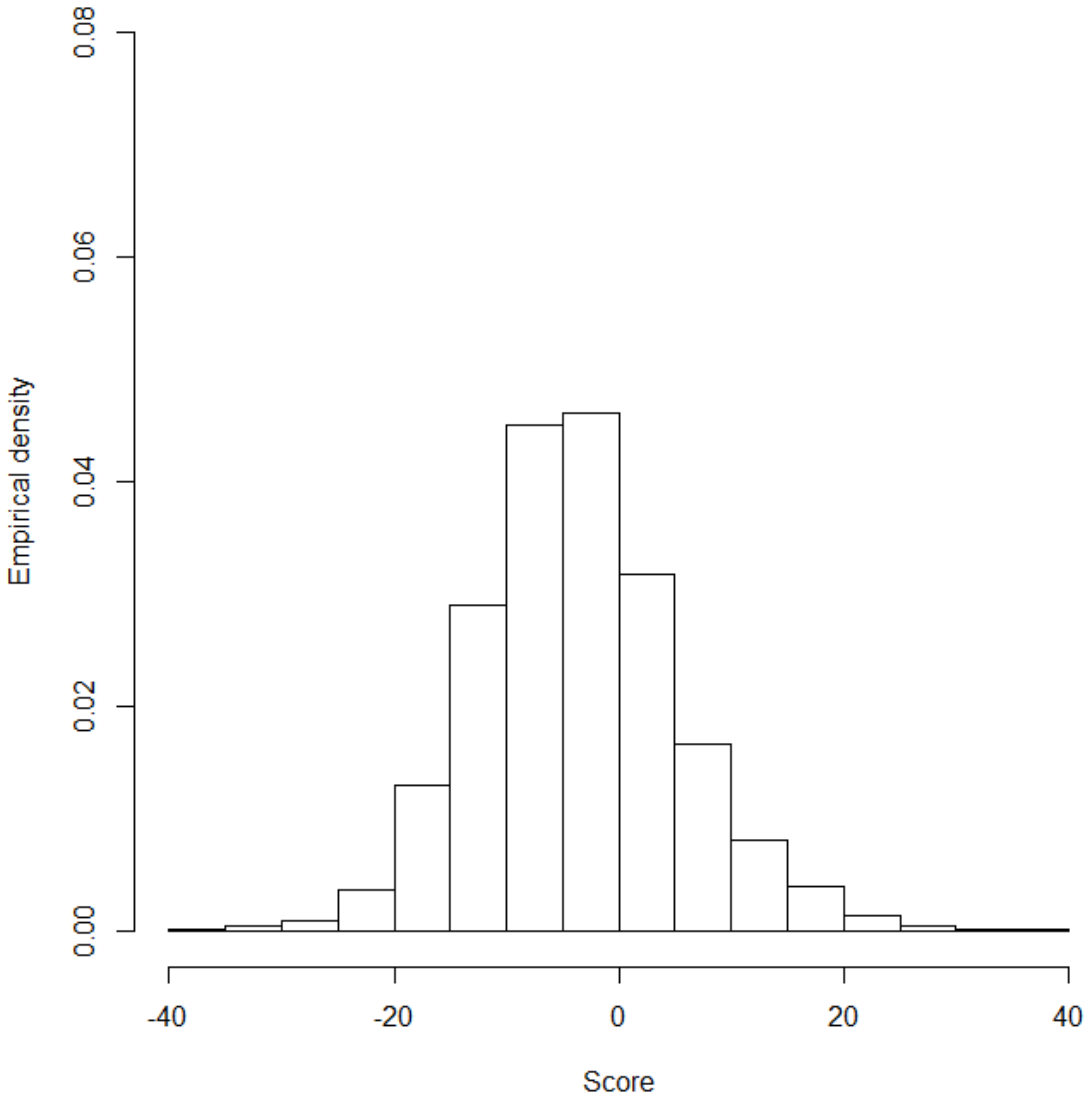


Figure 3-2B. Risk score distribution in the testing set, for the event of hospitalization in incident patients

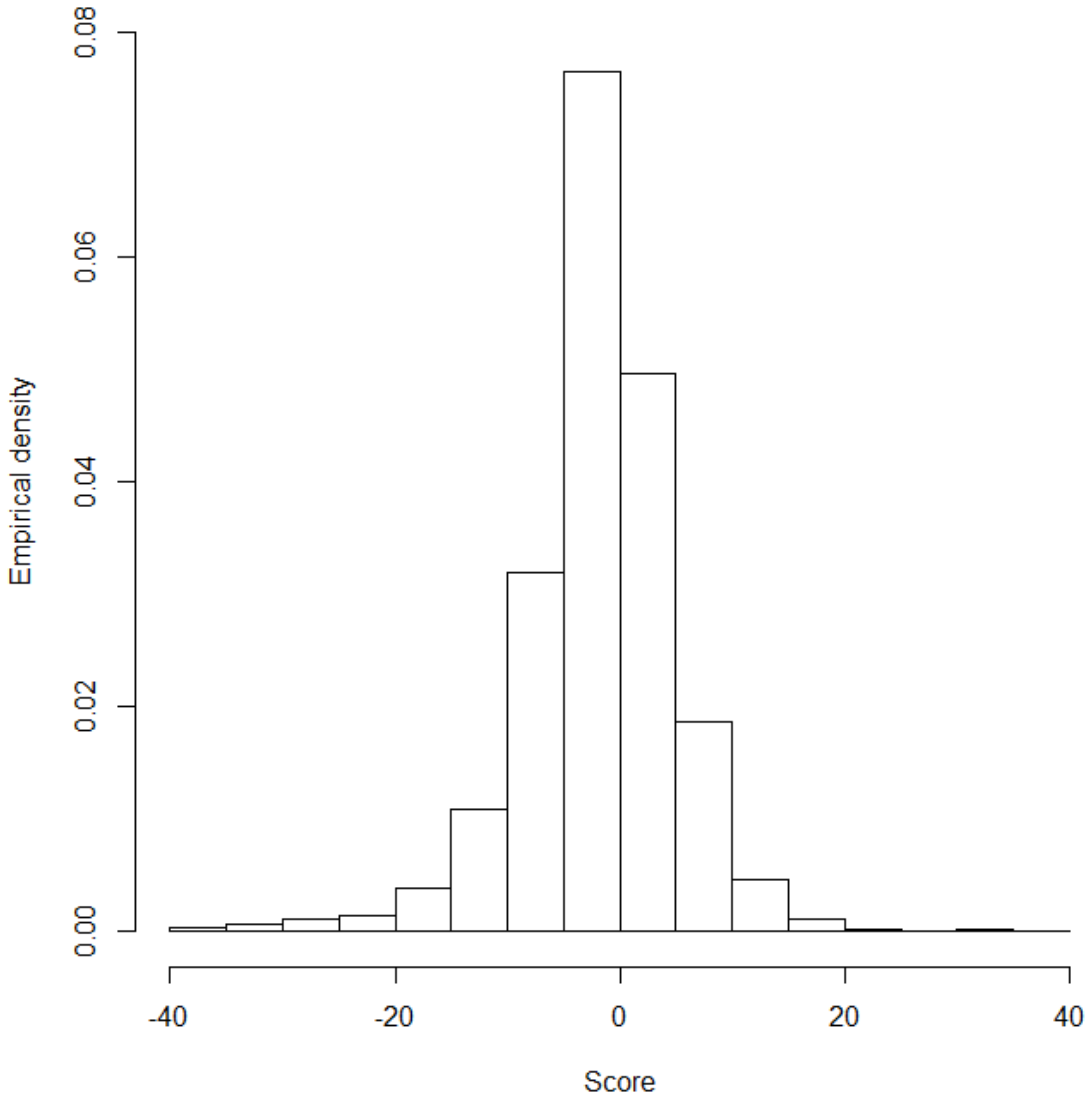


Figure 3-2C. Risk score distribution in the testing set, for the event of death in prevalent patients

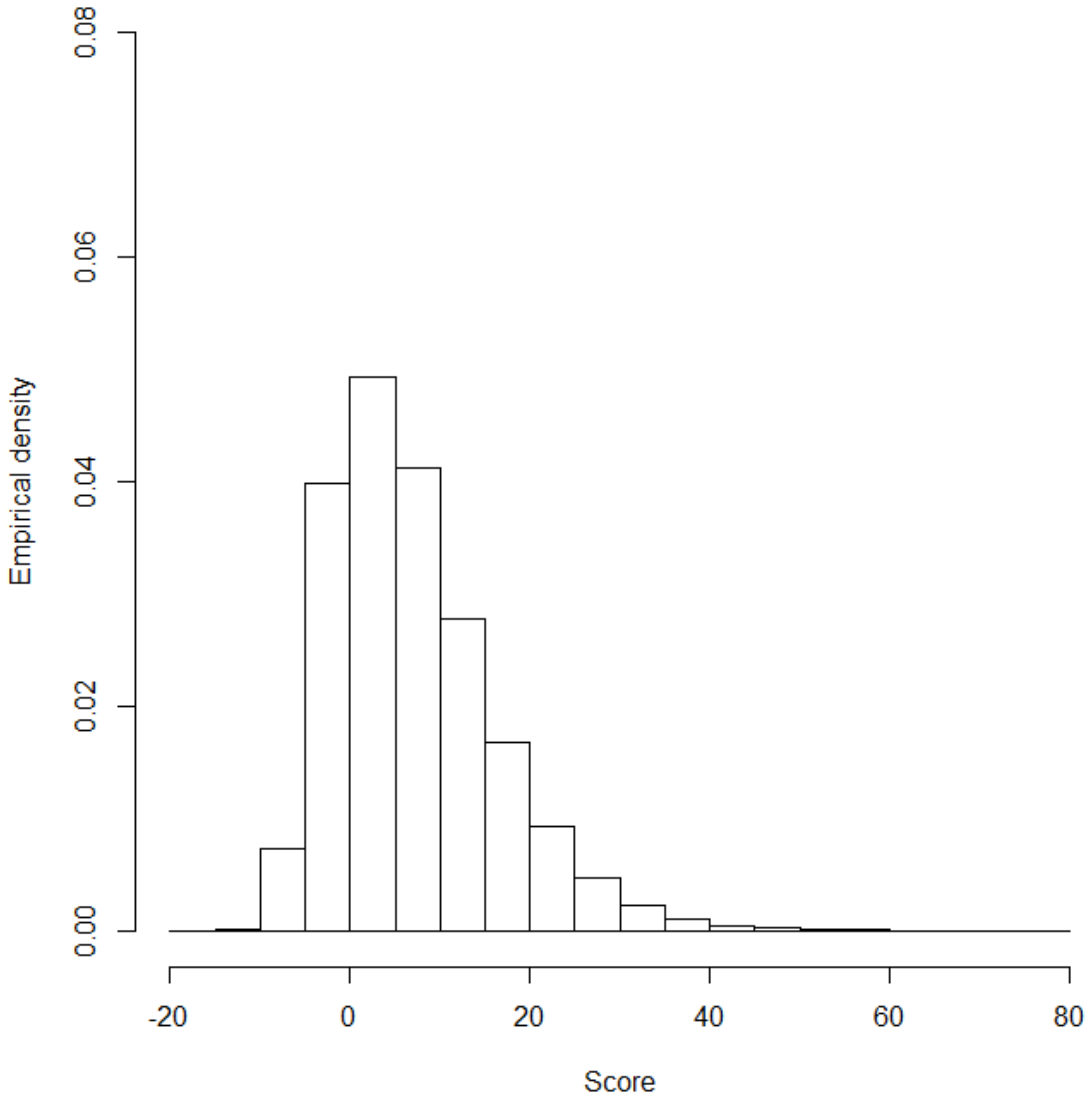


Figure 3-2D. Risk score distribution in the testing set, for the event of hospitalization in prevalent patients

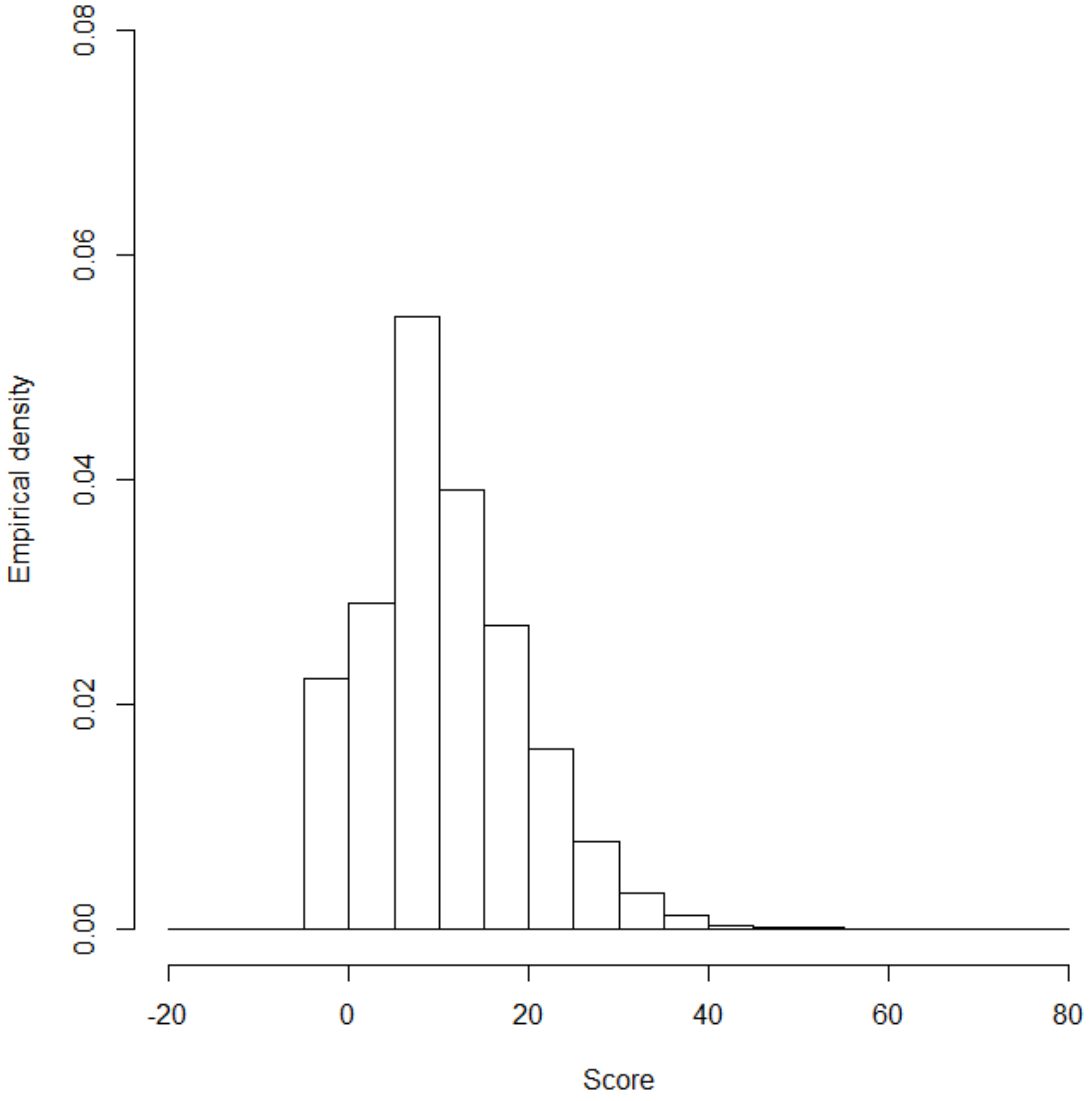


Figure 3-3A. Comparison of explained variation associated with risk score and combinations thereof in the testing set, for the event of death in incident patients

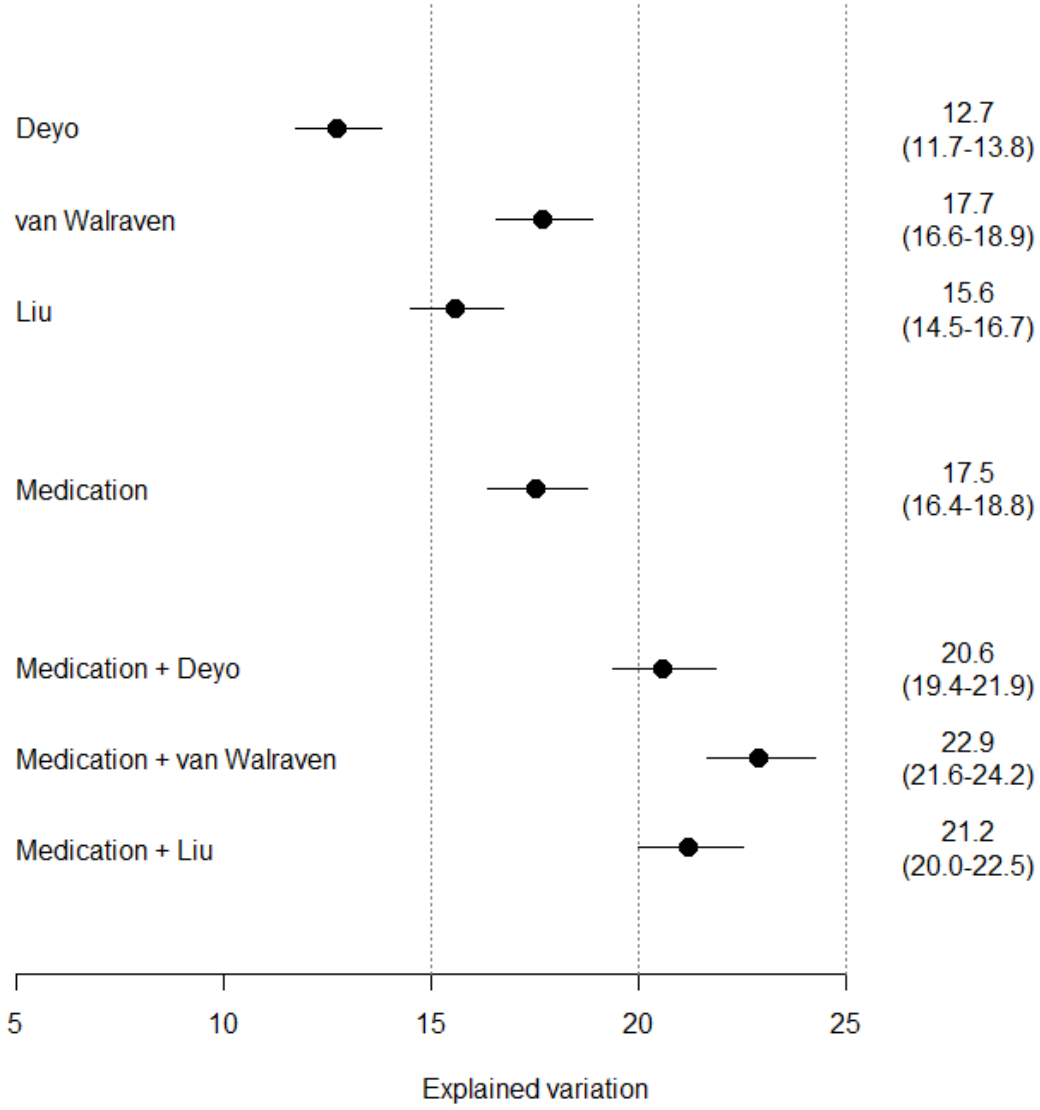


Figure 3-3B. Comparison of explained variation associated with risk score and combinations thereof in the testing set, for the event of hospitalization in incident patients

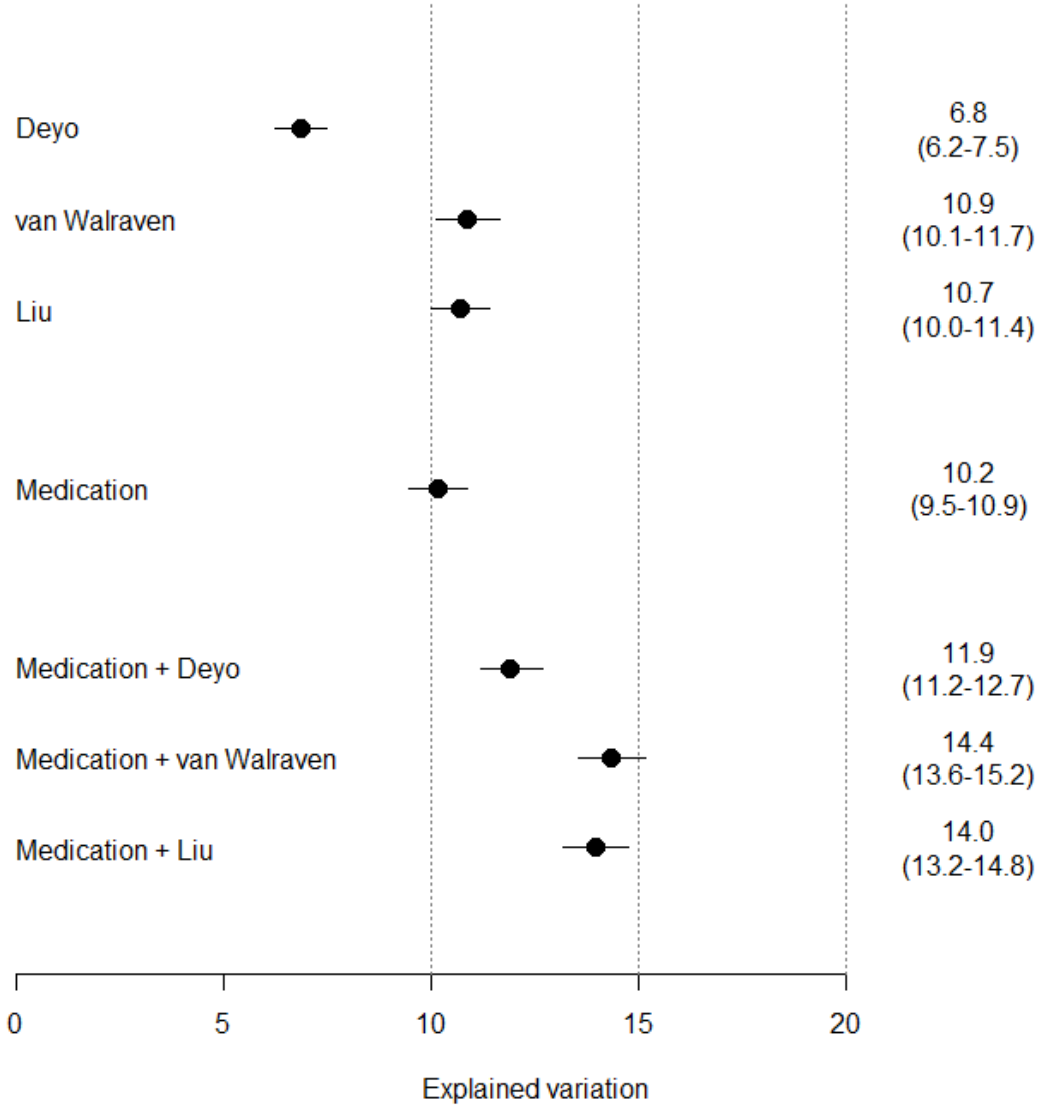


Figure 3-3C. Comparison of explained variation associated with risk score and combinations thereof in the testing set, for the event of death in prevalent patients

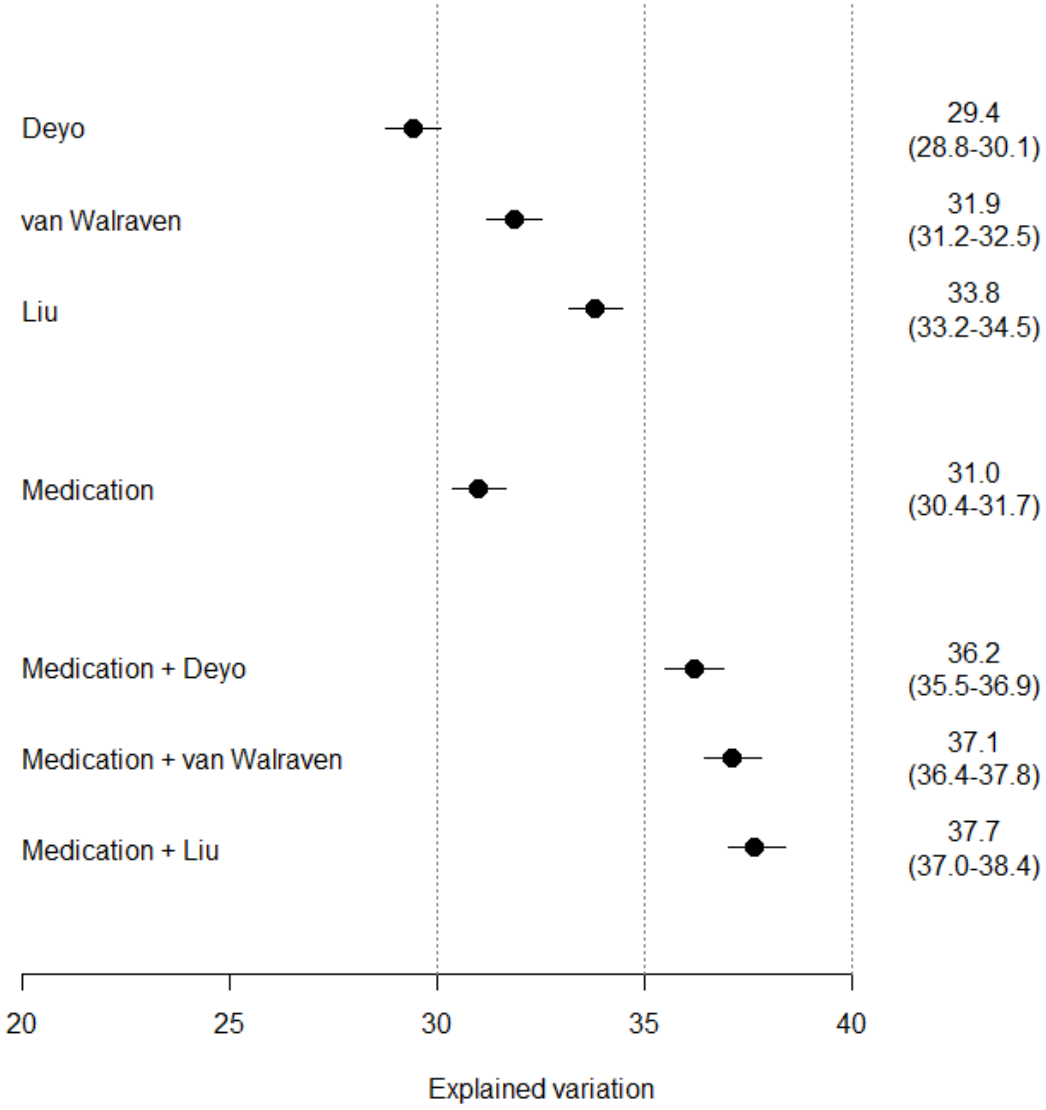
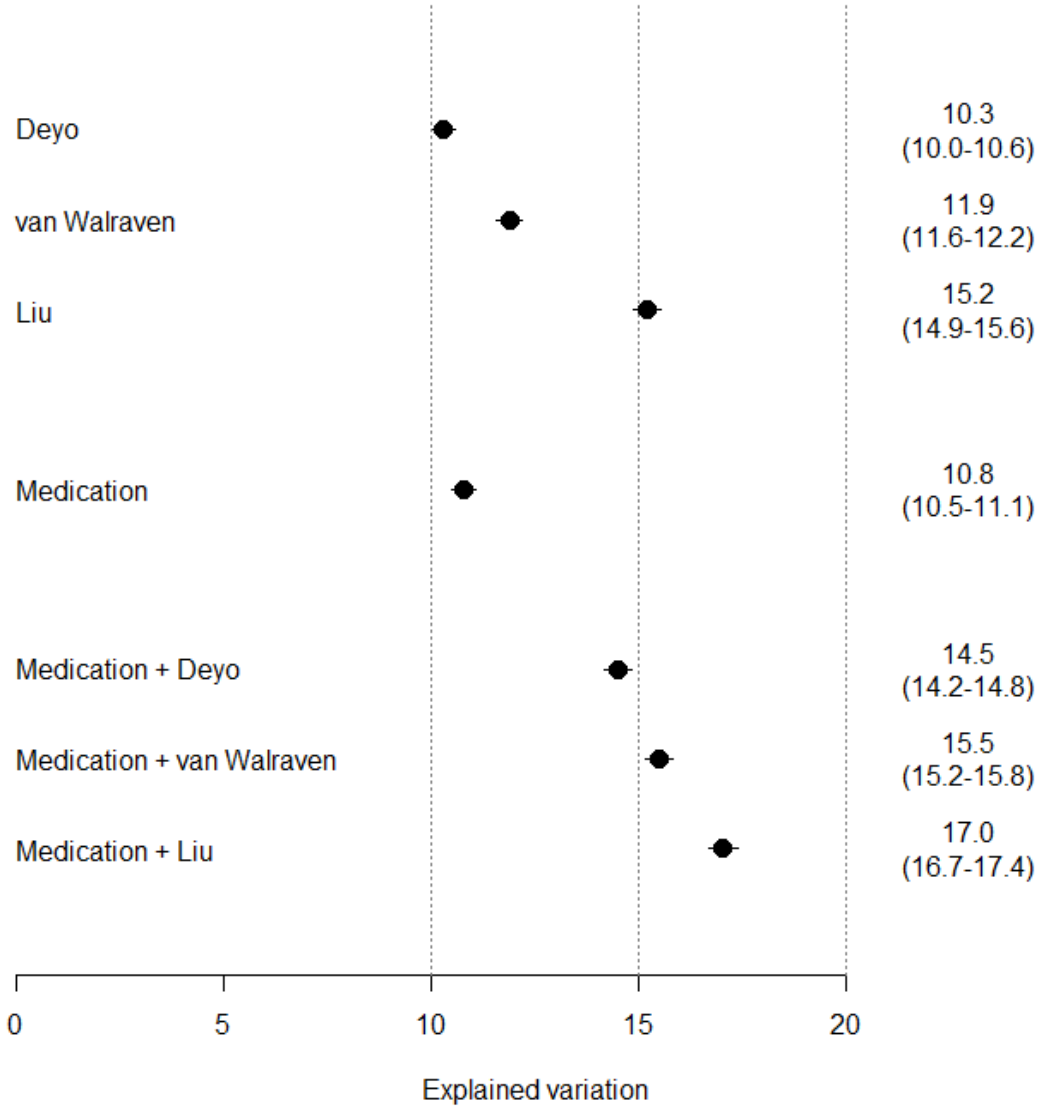


Figure 3-3D. Comparison of explained variation associated with risk score and combinations thereof in the testing set, for the event of hospitalization in prevalent patients



Chapter 4

Associations of Renin-Angiotensin System Inhibition with Mortality and Hospitalization in Dialysis Patients with Heart Failure

Abstract

Heart failure (HF) is a common comorbidity in chronic dialysis patients. Clinical practice guidelines in the general population recommend angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) for treatment of HF with reduced ejection fraction, but data supporting efficacy in dialysis patients are sparse. We used data from the United States Renal Data System to assess the relative hazards of death and hospitalization associated with renin-angiotensin system (RAS) inhibitor use in dialysis patients who had been discharged after hospitalization principally for HF. Discharges were ascertained from Medicare Part A claims between January 1, 2007, and December 31, 2011. RAS inhibitor treatment was ascertained from Part D claims during the 1 month following discharge. For each treated patient, we identified 2 propensity score-matched controls, according to demographic factors, comorbid conditions, in-hospital care, and discharge status. We applied both intention-to-treat (ITT) and on-treatment (OT) follow-up rules. There were 2407 treated patients and 4814 matched controls. Groups were generally balanced at discharge, but more patients with RAS inhibitor treatment were dispensed beta blockers (52.6% versus 16.8%). In ITT analysis, the adjusted hazard ratio (HR) of death for RAS inhibitor treatment was 0.86 (95% confidence interval, 0.78-0.94) and the adjusted HR for hospitalization was 0.90 (0.86-0.95). In OT analysis, the adjusted HR of death for RAS inhibitor treatment was 0.71 (0.62-0.82) and the HR of hospitalization was 0.89 (0.85-0.94). There were no significant

differences between ACE inhibitors and ARBs in the hazard of death, relative to matched controls, but only ACE inhibitors were associated with lower hazard of hospitalization. Interruption of RAS inhibitor treatment was common. In conclusion, RAS inhibitor treatment was associated with lower hazards of death and hospitalization in dialysis patients with HF, despite high incidence of treatment interruption.

Introduction

Heart failure (HF) is a common comorbidity in chronic dialysis patients. In one prospective study, 31% of new dialysis patients in 1982-1991 were diagnosed with HF.[51] By retrospective analysis, prevalence of HF was similar in new end-stage renal disease (ESRD) patients in 2010-2012.[52] In patients without HF at initiation of dialysis, subsequent loss of pump function is also likely. In the noted prospective study, 25% of new dialysis patients presented with *de novo* HF after a median of 15 months.[51] Anemia, vascular calcification, myocardial infarction, and persistent activation of the renin-angiotensin system (RAS) all complicate ESRD and may favor the development of HF. The combination of preexisting and *de novo* HF results in substantial burden on patients and payers; in 2011, prevalent dialysis patients were hospitalized for HF at a rate of more than 12 admissions per 100 patient-years.[53]

In patients with HF and normal kidney function, the efficacy of pharmacologic inhibition of the RAS is strongly supported by randomized trials. Clinical practice guidelines indicate that angiotensin-converting enzyme (ACE) inhibitors are recommended for patients with HF and ejection fraction (EF) less than 40%; angiotensin-receptor blockers (ARBs) are recommended in such patients who do not tolerate ACE inhibitors and are further characterized as "reasonable alternatives" to ACE inhibitors as first-line therapy.[54] For patients with HF and preserved EF, guidelines are limited. Specifically, ARBs might be considered to reduce risk of hospitalization, as was observed in the CHARM-Preserved trial of candesartan.[55] For dialysis patients with HF, evidence from trials is sparse. A trial of fosinopril versus placebo in hemodialysis patients with left ventricular hypertrophy reported non-significant reductions in cardiovascular risk,[56]

whereas a trial of dual therapy with telmisartan and an ACE inhibitor versus monotherapy with an ACE inhibitor in hemodialysis patients with HF and reduced ejection fraction reported significant reductions in cardiovascular risk.[57]

In this study, we used United States Renal Data System (USRDS) data to assess efficacy and safety of treatment with an ACE inhibitor or ARB in dialysis patients that were discharged from the hospital with a principal diagnosis of HF. Data regarding medication exposure were ascertained from Medicare Part D claims. Patients that were dispensed an ACE inhibitor or ARB were matched with patients that were dispensed neither an ACE inhibitor nor ARB, according to the propensity score for dispensation. For efficacy, we assessed all-cause death, cardiovascular death, sudden cardiac death, all-cause hospitalization, cardiovascular hospitalization, and HF hospitalization. For safety outcomes, we assessed angioedema and hyperkalemia.

Methods

Protection of Human Subjects

We analyzed USRDS data that were obtained by a Data Use Agreement with the National Institute of Diabetes and Digestive and Kidney Diseases. The study was reviewed by the Human Subjects Research Committee at Hennepin County Medical Center (Minneapolis, Minnesota).

Study Cohort

The source cohort included prevalent and incident dialysis patients. For the former, we retained patients with receipt of dialysis on December 31, 2007 (*i.e.*, index date); uninterrupted receipt of one dialytic modality (*i.e.*, either hemodialysis or

peritoneal dialysis) during 2007; date of initiation of renal replacement therapy no later than October 31, 2006; age between 20 and 100 years on the index date; and uninterrupted enrollment in Medicare Parts A and B during the 12-month interval immediately preceding the index date. For the latter, we retained patients with date of initiation of dialysis (*i.e.*, index date) between January 1, 2007, and December 31, 2009; age between 20 and 100 years on the index date; and uninterrupted enrollment in Medicare Parts A and B during the 12-month interval immediately preceding the index date. For both groups, we required non-missing data regarding race, sex, primary cause of ESRD, and ESRD Network of residence on the index date. We excluded patients with a hospitalization for HF (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] diagnosis code 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, or 428.*x* as principal diagnosis[5]) during the 12-month interval immediately preceding the index date.

We followed each patient from the index date to the earliest of death, kidney transplant, interruption of enrollment in Medicare Parts A and B, or December 31, 2011. During follow-up, we identified the first hospitalization for HF. We retained hospitalized patients with Medicare Part D enrollment during the 12-month interval immediately preceding the date of admission and with discharge to home, under self-care or supervision of a home health agency. To design the retrospective analogue of a washout period, we excluded patients who were dispensed an ACE inhibitor or ARB during the 3-month interval preceding the date of admission.

For sensitivity analyses, we repeated the cohort construction with alternative criteria regarding HF. For the first alternative, we identified during follow-up the first

hospitalization with either a principal or secondary diagnosis of HF. For the second alternative, we excluded patients with a hospitalization with either a principal or secondary diagnosis of HF during the 12-month interval immediately preceding the index date and we identified during follow-up the first hospitalization for HF.

Patient Characteristics

For each patient, we ascertained age, race, sex, primary cause of ESRD, ESRD duration, ESRD Network of residence, low-income subsidy (LIS) receipt, risk scores, body mass index (BMI), hematocrit, hospitalization history, kidney transplant wait-list status, erythropoiesis-stimulating agent (ESA) and intravenous vitamin D analogue (VDA) exposure, dialytic modality, dialysis provider, HF hospitalization factors (co-incident myocardial infarction and stroke, physician specialty care, diagnostic procedures, and length of stay), and discharge location. Age, ESRD duration, ESRD Network, LIS receipt, and wait-list status were identified at discharge. The risk scores comprised 2 comorbidity scores and 4 medication scores. For comorbidity, we used the Liu score and the van Walraven score of Elixhauser comorbid conditions.[59-60] In each score, we declared a condition to be present if we identified at ≥ 1 inpatient facility, skilled nursing facility, or home health agency claim or ≥ 2 outpatient facility or physician claims with qualifying ICD-9-CM diagnosis codes, as specified by Quan *et al*, during the 12 months preceding admission.[61-62] For medication, we used scores derived from dispensed medications during the 12 months preceding admission.[63] BMI and hematocrit were calculated from the means of measurements on outpatient dialysis and ESA claims, respectively, during the 6 months preceding admission. Hospitalization history was summarized by cumulative hospitalized days during the 6 months preceding

admission, whereas ESA and intravenous VDA exposure were summarized by cumulative doses during the 3 months preceding admission. Dialytic modality and dialysis provider were identified on the day before admission. During HF hospitalization, myocardial infarction was identified from ICD-9-CM diagnosis codes 410.*x*0 and 410.*x*1;[64] stroke was identified from codes 430.*x*, 431.*x*, 434.*x*, and 436.*x*.[65] Specialty care was identified from physician claims during hospitalization; diagnostic procedures were identified from both ICD-9-CM procedure codes on inpatient facility claims and *Current Procedural Terminology* (CPT) codes on physician claims during hospitalization.

Exposure

From Part D claims in the 1 month following discharge, we identified dispensed ACE inhibitors and ARBs, according to the National Drug Code and the associated Generic Product Identifier (GPI) code in the Medi-Span Master Drug Database (Indianapolis, IN). We included combination products containing an ACE inhibitor or ARB. We identified class-specific dates of first dispensation in the month and set the start of risk for exposed patients at the latest such date. We defined candidate controls as patients who were not dispensed an ACE inhibitor or ARB.

Matching

We used propensity score matching to select 2 matched controls per exposed patient.[66] We used logistic regression to model the probability of RAS inhibitor exposure among exposed patients and candidate controls. Covariates comprised the aforementioned patient characteristics; continuous covariates were parameterized with quadratic polynomials. From the fitted model, we estimated the propensity score (*i.e.*, probability) of exposure.

We ordered exposed patients according to number of days between discharge and start of risk and arbitrarily within each number of days. For each exposed patient with LIS *l*, propensity score *p*, and *d* days between discharge and start of risk, we selected a candidate control with LIS *l* and propensity score *q*, such that the absolute difference of *p* and *q* was minimized. We set the start of risk for the matched control at *d* days after discharge. The matched control was removed from further consideration in matching. After we selected one matched control for each exposed patient, we repeated the algorithm and identified another matched control.

Between discharge and the start of risk, we identified incidence of re-hospitalization and dispensation of beta blockers and digoxin.

Outcomes

We followed all patients from the start of risk to the earliest of death; kidney transplant; interruption of enrollment Medicare in Parts A, B, and D; or December 31, 2011. We identified the incidence of all-cause death; cardiovascular death; sudden cardiac death; hospitalization due to any cause, cardiovascular disease, HF, myocardial infarction, and stroke; angioedema; and hyperkalemia. Cardiovascular deaths were determined from the ESRD Death Notification and sudden cardiac deaths were determined from the ESRD Death Notification and inpatient facility claims.[67] Cardiovascular hospitalization was defined according to principal diagnosis codes, as specified by the USRDS.[52] Myocardial infarction and stroke were defined by principal diagnosis codes on inpatient facility claims. Angioedema and hyperkalemia were defined by diagnosis codes 995.1 and 276.7, respectively, on inpatient facility claims; for these events, we queried both principal and secondary diagnosis codes.

Statistical Analysis

We calculated statistical summaries of measured factors in exposed patients and matched controls. We assessed the match quality with absolute standardized differences; differences less than 10% indicate sufficient similarity to obviate adjustment.[68] We used intention-to-treat (ITT) and on-treatment (OT) rules during follow-up. For the ITT rule, we followed patients from the start of risk to the earliest of death; kidney transplant; interruption of enrollment Medicare in Parts A, B, and D; or December 31, 2011. For the OT rule, we added change in RAS inhibitor exposure to the list of dates on which follow-up may end. Specifically, change in exposure was defined at the end of the first 2-month interval without supply of an RAS inhibitor (in exposed patients) or 2 months after first dispensation of an RAS inhibitor (in matched controls).

For mortality outcomes, we estimated cumulative incidence for exposed patients and matched controls. To compare incidence in these groups, we used Cox proportional hazards regression to estimate relative hazard; the model was stratified by matched cluster. The model was adjusted for the incidence of re-hospitalization between discharge and start of risk and the concomitant dispensation of beta blockers and digoxin, because these factors were not included in the propensity score function. Because of modest differences between exposed patients and matched controls, the model was also adjusted for co-incident myocardial infarction, cardiology care during hospitalization, and use of coronary catheterization, echocardiogram, and myocardial perfusion scintigraphy during hospitalization. For hospitalization outcomes, we used Andersen-Gill regression to estimate the relative hazard of admission in exposed patients versus matched controls; the model was stratified by matched cluster. We used the robust sandwich estimator to model

covariance among recurrent hospitalizations. The model was adjusted for the same factors in models of mortality outcomes. However, for angioedema, the model was unadjusted, because of the low number of events. Finally, we estimated the cumulative incidence of exposure status crossover, with death as a competing risk.

For exploratory analysis, we estimated relative hazards of mortality and hospitalization for ACE inhibitor users and ARB users versus respective matched controls. For this analysis, we excluded matched clusters with an exposed patient that was dispensed both an ACE inhibitor and an ARB. Models were parameterized as previously described, but included additional adjustment for age, transplant wait-list status, medication scores for incident patients, and pulmonology care during hospitalization.

All analyses were conducted in SAS, version 9.2 (Cary, North Carolina), except for the exposure status crossover analysis, which was conducted in R, version 3.1.2 (Vienna, Austria).

Results

We identified 11,635 hospitalized cases of HF. There were 2407 (20.7%) patients who were dispensed an RAS inhibitor in the 1 month following discharge and 9228 patients who were not. From the latter subset, we identified 4814 matched controls. The characteristics of exposed patients and matched controls are displayed in Table 4-1. In exposed patients, mean age was 65.4 (standard deviation, 13.8) years, 52.4% were white, 42.7% were black, and mean ESRD duration was 4.8 (4.4) years. Mean hospitalized days during the 6 months before HF hospitalization and mean days during HF hospitalization

were 6.9 (12.6) and 4.7 (3.8), respectively. Most patients saw a cardiologist in the hospital (84.3%), but only 31.6% underwent an echocardiogram. Over 80% were discharged to home and nearly all (96.5%) received hemodialysis. Matching balanced all factors included in the propensity score (absolute standardized differences < 10%). However, there were differences in care between discharge and start of risk. Relative to matched controls, exposed patients were more likely to have been re-hospitalized (9.6% versus 5.9%), dispensed beta blockers (52.6% versus 16.8%), and dispensed digoxin (3.4% versus 1.3%).

Event counts and crude event rates are displayed in Table 4-2. In ITT follow-up, exposed patients and matched controls accumulated 3762 and 7035 patient-years, respectively (1.56 and 1.46 years per patient). There were 1123 deaths in exposed patients (proportion, 46.7%) and 2344 deaths in matched controls (48.7%); corresponding crude mortality rates were 30 and 33 deaths per 100 patient-years. Slightly less than 50% of deaths in each group were attributable to cardiovascular disease and slightly less than 30% were attributable to sudden cardiac death. There were 10,906 and 22,545 hospital admissions in exposed patients and matched controls, respectively; corresponding crude rates were 290 and 320 admissions per 100 patient-years. Nearly 40% of admissions in each group were for cardiovascular disease. Crude rates of both myocardial infarction and hyperkalemia were lower in exposed patients, while rates of both stroke and angioedema were higher. In OT follow-up, exposed patients and matched controls accumulated 1745 and 5207 patient-years, respectively (0.73 and 1.08 years per patient). There were 473 and 1811 deaths in exposed patients and matched controls, respectively; corresponding crude mortality rates were 27 and 35 deaths per 100 patient-years. Crude

hospitalization rates were 291 and 309 admissions per 100-patient years for exposed patients and matched controls, respectively. Rates of myocardial infarction, stroke, and angioedema were higher in exposed patients, but the rate of hyperkalemia was lower.

Estimates of cumulative incidence of death are displayed in Figures 4-1A and 4-1B. In ITT analysis, cumulative incidence for exposed patients versus matched controls was 8.4% versus 9.9% at 3 months, 15.0% versus 17.2% at 6 months, 26.2% versus 30.6% at 1 year, 44.7% versus 49.0% at 2 years, and 59.5% versus 61.1% at 3 years (Figure 4-1A). In OT analysis, incidence for exposed patients versus matched controls was 8.5% versus 9.9% at 3 months, 14.5% versus 17.4% at 6 months, 23.5% versus 30.9% at 1 year, 38.1% versus 49.7% at 2 years, and 51.7% versus 61.6% at 3 years (Figure 4-1B). Estimates of cumulative incidence of cardiovascular death are displayed in Figures 4-2A and 4-2B. In ITT analysis, cumulative incidence for exposed patients versus matched controls was 12.8% versus 14.7% at 1 year, 21.4% versus 23.4% at 2 years, and 29.0% versus 29.0% at 3 years (Figure 4-2A). Estimates of cumulative incidence of sudden cardiac death are displayed in Figures 4-3A and 4-3B. In ITT analysis, cumulative incidence for exposed patients versus matched controls was 7.3% versus 8.1% at 1 year, 12.7% versus 13.5% at 2 years, and 17.9% versus 17.0% at 3 years (Figure 4-3A). In OT analyses of both cardiovascular and sudden cardiac death, the lower incidence in exposed patients persisted through 4 years.

Adjusted hazard ratios of mortality and hospitalization are displayed in Table 4-3. In ITT analysis, the hazard ratio (HR) of death for exposed patients versus matched controls was 0.86 (95% confidence interval, 0.78-0.94). HRs of cardiovascular and sudden cardiac death were similar in magnitude. The HR of hospitalization for exposed

patients versus matched controls was 0.90 (0.86-0.95). HRs of admission for cardiovascular disease and HF were attenuated. HRs of both myocardial infarction and stroke were imprecise. The hazard of angioedema was nearly 2 times greater in exposed patients than matched controls, but the HR of hyperkalemia was 0.84 (0.76-0.94). In OT analysis, the HR of death controls was 0.71 (0.62-0.82), while the HR of hospitalization was 0.89 (0.85-0.94). HRs of admission for cardiovascular disease and HF were again attenuated. The hazard of angioedema was more than 4 times greater in exposed patients than matched controls, but the HR of hyperkalemia again favored exposed patients.

Full models of mortality and hospitalization in ITT analysis are displayed in Table 4-4. For mortality, cardiologist care during hospitalization (adjusted HR, 1.22), early re-hospitalization (1.35), and digoxin dispensation (1.51) were each strongly associated with mortality risk. On the other hand, beta blocker dispensation (1.08) was weakly associated. For hospitalization, early re-hospitalization (1.37) and digoxin dispensation (1.20) were strongly associated with admission risk, but other factors, including beta blocker dispensation (0.97), were not strongly associated.

The cumulative incidence of change in exposure status is displayed in Figure 4-4. Incidence of the interruption of RAS inhibitor exposure in exposed patients versus initiation of exposure in matched controls was 22.3% versus 0.8% at 1 month, 33.6% versus 9.2% at 3 months, 45.7% versus 16.1% at 6 months, 58.5% versus 23.7% at 1 year, 67.3% versus 31.5% at 2 years, and 71.0% versus 35.0% at 3 years.

Subclass Associations

Among 2407 exposed patients, 1881 (78.1%) were dispensed an ACE inhibitor, 466 (19.4%) were dispensed an ARB, and 60 (2.5%) were dispensed both. The

characteristics of exposed patients that received monotherapy and respective matched controls are displayed in Table 4-5, with stratification by subclass of monotherapy. ACE inhibitor users and matched controls were similar with respect to factors included in the propensity score, but they were different with respect to other factors. Relative to matched controls, ACE inhibitor users were more likely to have been re-hospitalized (9.5% versus 5.5%), dispensed beta blockers (53.3% versus 16.0%), and dispensed digoxin (3.4% versus 1.5%). ARB users and matched controls were generally similar with respect to factors included in the propensity score, although the prevalence of blacks was modestly lower in users and the prevalence of myocardial infarction during HF hospitalization was modestly higher. Relative to controls, users were more likely to have been dispensed beta blockers (48.1% versus 18.7%) and digoxin (3.0% versus 1.5%).

Subclass-specific adjusted hazard ratios of mortality and hospitalization are displayed in Table 4-6. In ITT analysis, the HR of death for ACE inhibitor users versus matched controls was 0.90 (0.80-1.00), whereas the HR for ARB users versus matched controls was 0.83 (0.67-1.01); the difference between HRs was compatible with random variation ($P = 0.11$). In OT analysis, the HR for ACE inhibitor users versus controls was 0.77 (0.66-0.90), whereas the HR for ARB users versus controls was 0.73 (0.54-0.99); the difference was compatible with random variation ($P = 0.11$). Regarding hospitalization, in ITT analysis, the HR of admission for ACE inhibitor users versus controls was 0.89 (0.86-0.92), whereas the HR for ARB users versus controls was 1.00 (0.94-1.07); the difference was statistically significant ($P < 0.01$). Regarding hospitalization for cardiovascular disease, the HR of admission for ACE inhibitor users versus controls was 0.91 (0.86-0.96), whereas the HR for ARB users versus controls was 1.05 (0.94-1.16); the

difference was also statistically significant ($P < 0.01$). Results from OT analysis were qualitatively similar.

Sensitivity Analyses

In the first analysis, the case definition was widened to include index hospital admissions with either a primary or secondary diagnosis of HF. The results of this analysis are displayed in Tables 4-7 and 4-8. We identified 3439 exposed patients and 6878 controls. The groups were similar with respect to factors included in the propensity score. However, relative to matched controls, early re-hospitalization and dispensation of beta blockers and digoxin were more likely in exposed patients than controls. In ITT analysis, the mortality HR for exposed patients versus controls was 0.88 (0.81-0.96), whereas the hospitalization HR was 0.92 (0.88-0.95). In OT analysis, corresponding HRs were 0.79 (0.70-0.89) for death and 0.92 (0.88-0.96) for hospitalization. In the second analysis, the case definition was narrowed to exclude patients with a history of hospital admissions with either a primary or secondary diagnosis of HF. The results of this analysis are displayed in Tables 4-9 and 4-10. We identified 1774 exposed patients and 3548 controls. The ITT HR of death for exposed patients versus controls was 0.79 (0.70-0.89), whereas the HR of hospitalization was 0.87 (0.82-0.93). In OT analysis, corresponding HRs were 0.71 (0.60-0.84) for death and 0.85 (0.79-0.91) for hospitalization.

Discussion

Heart failure is a common cause of morbidity in dialysis patients. According to the Peer Report, in 2010-2011, the hospitalization rate for HF was between 15.5 and 20.6

admissions per 100 patient-years during 1 year after dialysis initiation and between 12.4 and 15.7 admissions per 100 patient-years in prevalent dialysis patients; moreover, the 30-day rate of re-hospitalization after discharge from hospitalization principally for HF was 36.5%, roughly 1.5 times the rate observed in Medicare beneficiaries without ESRD.[53,69] In the broader population, ACE inhibitors and ARBs are strongly recommended for treatment of HF with reduced EF.[54] Whether these agents are similarly effective in dialysis patients is unclear. In this study, we used Medicare claims data to assess relative hazards of death and hospitalization in patients who were dispensed an ACE inhibitor or ARB shortly after discharge from hospitalization principally for HF and in matched controls. With adjustment for concomitant use of beta blockers and digoxin, we found that treatment with an ACE inhibitor or ARB was associated with 14% lower risk of death and 10% lower risk of hospitalization in intention-to-treat analysis. With more specific criteria for hospitalized cases, associations were stronger in magnitude. Although angioedema was relatively more likely to occur in treated patients, hyperkalemia, a problematic side effect of ACE inhibitors and ARBs, was not. Regarding the subclasses, we found that ACE inhibitors and ARBs were similarly associated with lower hazard of death, but that only ACE inhibitors were associated with lower hazard of hospitalization.

The efficacy of ACE inhibitors for the treatment of HF was conclusively demonstrated in the Studies of Left Ventricular Dysfunction (SOLVD), where patients with EF $\leq$ 35% were randomized to receive either 20 mg/day of enalapril or placebo.[70] Patients receiving enalapril had 16% lower risk of death and 26% lower risk of death or hospitalization due to HF. Later trials of captopril (SAVE), ramipril (AIRE), and

trandolapril (TRACE) collectively established the efficacy of ACE inhibitors for the treatment of heart failure after myocardial infarction.[71-73] The efficacy of ARBs was first demonstrated in the Valsartan Heart Failure Trial (Val-HeFT), where stable patients with New York Heart Association class II, III, or IV HF were randomized to receive either 320 mg/day of valsartan or placebo.[74] Patients receiving valsartan had 20% lower risk of the composite of death, hospitalization due to HF, cardiac arrest (with resuscitation), or intravenous administration of inotropic or vasodilator medications. Later, the CHARM-Added trial showed that treatment with candesartan, on top of an ACE inhibitor, reduced the risk of cardiovascular death or hospitalization due to HF by 15% in patients with class II, III, or IV HF and ejection fraction $\leq 40\%$; the CHARM-Alternative trial indicated similar efficacy of valsartan (versus placebo) in patients with ACE inhibitor intolerance.[75-76] All of these trials, however, were conducted in patients with reduced EF. Meta-analysis of trials in patients with HF and preserved EF indicates no benefit with inhibition of the renin-angiotensin system.[77] This may be an important distinction for interpretation of our study, as we were unable to differentiate systolic from diastolic heart failure. Recent USRDS data suggest that systolic and diastolic heart failure may be equally prevalent in dialysis patients.[78] Plausibly, our results may understate the benefit of treatment in patients with reduced EF and overstate the benefit in those with preserved EF.

One trial of ACE inhibition has been completed in dialysis patients. In the Fosinopril in Dialysis (FOSIDIAL) study, 397 hemodialysis patients with left ventricular hypertrophy were randomized to receive either 20 mg/day of fosinopril or placebo; the mean achieved dose in the trial was 13.2 mg/day.[56] The primary endpoint was a

composite of cardiovascular death, nonfatal myocardial infarction, unstable angina, stroke, revascularization, hospitalization due to HF, or cardiac arrest (with resuscitation). In intention-to-treat analysis, the hazard ratio of the composite for fosinopril versus placebo was 0.93 (0.68-1.26); in a per-protocol analysis of 380 patients, the corresponding hazard ratio was 0.80 (0.59-1.10). Despite the difference between left ventricular hypertrophy and hospitalization principally for HF, as well as differences in outcomes, the risk ratios in FOSIDIAL are similar in magnitude to the hazard ratios in our study. However, we did not find identify strong associations of treatment with risk of ischemic events. This suggests that the primary benefit of RAS inhibition may be in the reduction of arrhythmias preceding sudden cardiac death (SCD). Notably, we found that inhibition of the RAS was associated with 16% and 29% lower hazards of SCD in ITT and OT analyses, respectively.

Whether ACE inhibitors and ARBs are equally efficacious for the treatment of HF has been contested. In a meta-analysis of trials comparing ARBs to ACE inhibitors in patients with HF and EF $\leq$ 40%, there were no significant differences between subclasses in rates of death and hospitalization.[79] We found some quantitative differences in mortality hazard ratios between ACE inhibitors and ARBs, although differences were compatible with random variation. In ITT analyses of death and cardiovascular death (but not SCD), HRs associated with ACE inhibitors versus no treatment were attenuated, relative to corresponding HRs associated with ARBs versus no treatment. It is interesting to speculate whether the pharmacokinetics of ACE inhibitors and ARBs may be relevant, as the former (excluding fosinopril) are removed by hemodialysis and the latter are not.[80] Recently, Weir *et al* reported that initiation of high-dialyzability versus low-dialyzability

beta blockers was acutely associated with excess risk of death.[81] On the other hand, we found that only ACE inhibitors were associated with lower risk of hospitalization. However, this discrepancy may be attributable to informative censoring, as the lower risk of death in ARB-treated patients may have progressively engendered a subset that was in relatively poor health, but alive. Inverse probability-of-censoring weighting is needed to clarify these results.[82]

Unsurprisingly, we found that the cumulative incidence of treatment interruption for > 2 months was high. Notably, more than 22% of patients who were dispensed an ACE inhibitor or ARB discontinued treatment after 1 month, *i.e.*, in most cases, after the first 30-day supply was used. By 6 and 12 months, roughly 46% and 59% of exposed patients discontinued treatment. Polypharmacy is common in dialysis patients and adherence to oral medications is generally low.[83] These data do not necessarily indicate that ACE inhibitors and ARBs are poorly tolerated by dialysis patients. In fact, beta blockers, calcium channel blockers, ACE inhibitors, and ARBs are all widely used.[28] Instead, these data suggest that the therapeutic potential of RAS inhibition in HF may be constrained by the degree to which patients simply refill medication. Delivery of oral medications to dialysis facilities may be a useful first step.[84]

This study has important limitations. First, as with all observational studies, unmeasured confounding may be present, despite use of propensity score matching. In light of the relatively high incidence of death in exposed patient and matched controls, it is possible that physicians prescribed ACE inhibitors and ARBs to patients that were in better health and perceived to benefit from treatment. Second, we were unable to describe the nature and severity of HF during the index hospitalization. Medicare claims during

the study era rarely differentiated between systolic and diastolic heart failure and ejection fraction is not recorded. Third, risk was assessed after HF had necessitated hospitalization. Whether the benefits and risks associated with inhibition of the RAS after initial diagnosis of HF in the outpatient setting are the same as in our study is unclear and thus merits further study. Finally, concomitant use of beta blockers in patients who were dispensed an ACE inhibitor or ARB poses a challenge to interpretation of study findings. We adjusted for the baseline difference in early exposure to beta blockers; for that matter, because beta blockers were weakly associated with risks of death and hospitalization, adjustment was relatively unimportant. However, adjustment does not preclude the possibility that the survival advantage in exposed patients was partially due to synergistic effects of ACE inhibitors and ARBs with beta blockers.[85]

In conclusion, this study suggests that pharmacologic inhibition of the renin-angiotensin system is associated with reduced risk of death and hospitalization in dialysis patients with HF. Unknown is whether this association is limited to patients with systolic heart failure. Studies with finer definitions of heart failure are needed. This study reassuringly suggests that the risk of hyperkalemia necessitating hospitalization is not higher with ACE inhibitor or ARB treatment. However, to the extent that ACE inhibitors and ARBs are efficacious in heart failure on dialysis, there is clearly room to improve rates of prescription and persistence. Only 1 in 5 patients were dispensed an ACE inhibitor or ARB within 30 days of discharge to home or home health care, and among patients who were dispensed medication, 1 in 5 discontinued treatment after 1 month of treatment. Strategies to increase use of these agents may directly improve outcomes in chronic dialysis patients.

Table 4-1. Characteristics of candidate controls, matched controls, and exposed patients, among heart failure cases ascertained from the principal diagnosis

	Candidate controls	Matched controls	Exposed patients	ASD [a]
Sample size	9228	4814	2407	
Age [b] (years)	65.9 (14.0)	65.4 (13.9)	65.4 (13.8)	0.0
Race (%)				
White	56.2	51.4	52.4	1.9
Black	38.8	43.7	42.7	2.1
Native American	1.1	0.9	1.1	1.5
Asian	3.4	3.6	3.5	0.3
Other	0.4	0.4	0.3	0.4
Sex (%)				
Female	50.1	49.3	49.4	0.3
Male	49.9	50.7	50.6	0.3
Primary cause of ESRD (%)				
Diabetes	43.6	42.7	42.7	0.1
Hypertension	32.1	33.8	33.3	1.0
Polycystic kidney disease	9.1	9.2	9.6	1.1
Glomerulonephritis	2.0	1.7	1.7	0.2
Other cause	10.1	9.6	9.5	0.4
Unknown cause	3.3	3.0	3.2	1.2
ESRD duration [b] (years)	5.1 (4.5)	4.8 (4.3)	4.8 (4.4)	1.0
Low-income subsidy reciept [b] (%)				
Not subsidized	30.4	26.8	26.8	0.0
Subsidized, without Medicaid	10.4	10.9	10.9	0.0
Subsidized, with Medicaid	59.2	62.2	62.2	0.0
Risk scores [c]				
Liu score	7.1 (4.1)	6.4 (4.0)	6.3 (4.0)	2.3
van Walraven score	17.9 (9.9)	16.5 (9.7)	16.3 (9.7)	1.8
Medication score 1	-5.3 (8.7)	-6.6 (8.7)	-6.7 (8.6)	0.5

Medication score 2	-5.7 (8.9)	-6.6 (8.5)	-6.6 (8.9)	0.0
Medication score 3	10.0 (9.3)	8.5 (8.5)	8.5 (8.5)	0.8
Medication score 4	13.2 (8.7)	12.1 (8.2)	12.1 (8.2)	0.6
Body mass index [d] (kg / m^2)	28.2 (7.1)	27.3 (6.5)	27.4 (6.5)	0.8
Hematocrit [e] (%)	33.8 (3.0)	33.7 (3.1)	33.7 (3.0)	0.3
Hospitalization history [d] (days)	8.2 (13.9)	6.9 (12.2)	6.9 (12.6)	0.6
Kidney transplant waitlist registration [b] (%)	11.3	11.9	11.9	0.0
ESA exposure [e]				
No exposure (%)	7.0	7.5	7.9	1.5
Darbepoetin alfa dose [f] (mcg)	744 (709)	772 (775)	823 (819)	6.4
Epoetin alfa dose [f] (1000s IU)	230 (222)	223 (213)	223 (213)	0.0
Intravenous VDA exposure [e]				
No exposure (%)	21.8	21.0	21.3	0.9
Calcitriol dose [f] (mcg)	33 (28)	38 (29)	34 (26)	15.3
Doxercalciferol dose [f] (mcg)	128 (86)	130 (85)	135 (85)	5.3
Paricalcitol dose [f] (mcg)	170 (139)	172 (139)	173 (139)	0.9
Dialytic modality [b] (%)				
Hemodialysis	97.3	96.7	96.5	1.5
Peritoneal dialysis	2.7	3.3	3.5	1.5
Dialysis provider [b] (%)				
Fresenius Medical Care	35.7	34.9	34.9	0.0
DaVita	27.9	27.9	27.6	0.7
Dialysis Clinic, Inc. (DCI)	3.3	3.0	3.0	0.1
Small dialysis organization	10.1	10.7	10.9	0.7
Independent dialysis provider	14.5	15.4	15.5	0.2
Hospital-based dialysis provider	8.3	7.8	7.8	0.0
Unknown affiliation	0.1	0.2	0.2	0.5
Co-incident cardiovascular morbidity [g] (%)				
Myocardial infarction	2.2	3.4	3.9	2.4
Stroke	0.2	0.3	0.3	0.8
Specialty care during HF hospitalization (%)				
Cardiologist	74.7	84.5	84.3	0.6
Nephrologist	84.1	86.3	86.5	0.8
Pulmonologist	18.1	19.0	18.6	1.1

Procedures during HF hospitalization (%)				
Coronary catheterization	6.8	12.3	15.7	9.8
Echocardiogram	23.2	31.4	31.6	0.5
Electrocardiogram	74.3	76.3	76.9	1.3
Exercise electrocardiography	6.2	10.4	11.6	3.9
Myocardial perfusion scintigraphy	4.4	7.4	8.7	4.7
Length of stay [g] (days)	4.3 (3.9)	4.6 (3.8)	4.7 (3.8)	2.5
Discharge location (%)				
Home, under self-care	80.0	81.6	81.8	0.4
Home health agency	20.0	18.4	18.2	0.4
Early re-hospitalization [h] (%)		5.9	9.6	14.2
Concomitant exposure [h] (%)				
Beta blocker		16.8	52.6	81.0
Digoxin		1.3	3.4	13.6

Note: For quantities not displayed as percentages, summaries are displayed as mean and standard deviation (in parentheses).

Abbreviations: ASD, absolute standardized difference; HF, heart failure; ESA, erythropoiesis-stimulating agent; ESRD, end stage renal disease; IU, international units; VDA, vitamin D analogue.

[a] Difference between exposed patients and matched controls, in percentage of 1 standard deviation.

[b] At the start of risk.

[c] During the 12 months before admission for heart failure.

[d] During the 6 months before admission for heart failure.

[e] During the 3 months before admission for heart failure.

[f] Among patients with at least one administration.

[g] During hospitalization for heart failure.

[h] Between discharge and the start of risk.

Table 4-2. Event counts and crude event rates in exposed patients and matched controls, by follow-up rule

	Intention-to-treat		On-treatment	
	Matched controls	Exposed patients	Matched controls	Exposed patients
Patient-years at risk	7035	3762	5207	1745
Deaths				
All-cause	2344	1123	1811	473
	(33)	(30)	(35)	(27)
Cardiovascular	1119	545	863	238
	(16)	(14)	(17)	(14)
Sudden cardiac	647	332	489	145
	(9.2)	(8.8)	(9.4)	(8.3)
Hospital admissions				
All-cause	22,545	10,906	16,118	5073
	(320)	(290)	(309)	(291)
Cardiovascular	8706	4230	6136	2178
	(124)	(112)	(118)	(125)
Heart failure	3542	1728	2492	950
	(50)	(46)	(48)	(54)
Cardiovascular events				
Myocardial infarction	577	285	415	152
	(8.2)	(7.6)	(8.0)	(8.7)
Stroke	207	135	146	61
	(2.9)	(3.6)	(2.8)	(3.5)
Safety events				
Angioedema	27	22	13	11
	(0.38)	(0.58)	(0.25)	(0.63)
Hyperkalemia	3731	1616	2450	682
	(53)	(43)	(47)	(39)

Note: For events, summaries are displayed as cumulative count and rate per 100 patient-years (in parentheses).

Table 4-3. Adjusted hazard ratios for exposed patients versus matched controls, by follow-up rule

	Intention-to-treat			On-treatment		
	HR	95% CI	*P*	HR	95% CI	*P*
Mortality						
All-cause	0.86	(0.78-0.94)	< 0.01	0.71	(0.62-0.82)	< 0.01
Cardiovascular	0.88	(0.77-1.01)	0.08	0.75	(0.62-0.91)	< 0.01
Sudden cardiac death	0.84	(0.70-1.01)	0.07	0.81	(0.63-1.05)	0.11
Hospitalization						
All-cause	0.90	(0.86-0.95)	< 0.01	0.89	(0.85-0.94)	< 0.01
Cardiovascular	0.94	(0.88-1.00)	0.04	0.95	(0.89-1.02)	0.19
Heart failure	0.95	(0.86-1.04)	0.24	1.00	(0.90-1.10)	0.95
Cardiovascular morbidity						
Myocardial infarction	0.91	(0.76-1.09)	0.30	1.08	(0.86-1.35)	0.53
Stroke	1.25	(0.95-1.62)	0.11	1.19	(0.85-1.67)	0.32
Safety						
Angioedema	1.91	(0.95-3.84)	0.07	4.12	(1.39-12.2)	0.01
Hyperkalemia	0.84	(0.76-0.94)	< 0.01	0.84	(0.74-0.96)	< 0.01

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

Table 4-4. Hazard ratios from models of all-cause mortality and all-cause hospitalization in intention-to-treat analysis

	HR	95% CI	*P*
All-cause mortality			
ACE inhibitor or ARB	0.86	(0.78-0.94)	< 0.01
Co-incident myocardial infarction	1.16	(0.88-1.53)	0.28
Cardiologist care during hospitalization	1.22	(1.04-1.42)	0.02
Procedures during hospitalization			
Coronary catheterization	1.13	(0.93-1.38)	0.23
Echocardiogram	1.12	(1.00-1.25)	0.06
Myocardial perfusion scintigraphy	1.04	(0.85-1.27)	0.70
Early rehospitalization	1.35	(1.11-1.65)	< 0.01
Concomitant exposure			
Beta blocker	1.08	(0.96-1.22)	0.21
Digoxin	1.51	(1.08-2.10)	0.02
All-cause hospitalization			
ACE inhibitor or ARB	0.90	(0.86-0.95)	< 0.01
Co-incident myocardial infarction	1.05	(0.92-1.20)	0.50
Cardiologist care during hospitalization	1.00	(0.92-1.08)	0.99
Procedures during hospitalization			
Coronary catheterization	0.97	(0.88-1.07)	0.57
Echocardiogram	0.97	(0.92-1.03)	0.35
Myocardial perfusion scintigraphy	1.09	(0.98-1.21)	0.10
Early rehospitalization	1.37	(1.22-1.54)	< 0.01
Concomitant exposure			
Beta blocker	0.97	(0.91-1.03)	0.30
Digoxin	1.20	(1.00-1.45)	0.05

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CI, confidence interval; HR, hazard ratio.

Table 4-5. Characteristics of ACE inhibitor-exposed patients, ARB-exposed patients, and respective matched patients, among heart failure cases ascertained from the principal diagnosis

	ACE inhibitor			ARB		
	Matched controls	Exposed patients	ASD [a]	Matched controls	Exposed patients	ASD [a]
Sample size	3762	1881		932	466	
Age [b] (years)	65.5 (13.9)	65.6 (13.6)	1.1	65.4 (14.1)	64.8 (14.5)	3.8
Race (%)						
White	51.8	52.5	1.3	50.6	53.0	4.7
Black	43.5	43.5	0.0	43.9	38.0	12.0
Native American	0.9	1.1	2.4	1.4	1.1	2.9
Asian	3.5	2.7	4.6	3.8	7.1	14.7
Other	0.3	0.2	2.1	0.3	0.9	7.0
Sex (%)						
Female	49.7	47.9	3.6	50.1	54.9	9.7
Male	50.3	52.1	3.6	49.9	45.1	9.7
Primary cause of ESRD (%)						
Diabetes	42.1	42.4	0.7	42.5	44.6	4.3
Hypertension	34.0	34.0	0.1	32.7	30.0	5.8
Polycystic kidney disease	9.7	9.0	2.1	8.9	11.4	8.2
Glomerulonephritis	1.8	1.8	0.0	1.7	1.7	0.0
Other cause	9.3	9.5	0.9	10.7	9.4	4.3
Unknown cause	3.2	3.3	0.3	3.4	2.8	3.7
ESRD duration [b] (years)	4.8 (4.4)	4.8 (4.3)	1.0	4.7 (4.0)	5.0 (4.4)	7.2
Low-income subsidy reciept [b] (%)						
Not subsidized	27.6	27.6	0.0	24.3	24.3	0.0
Subsidized, without Medicaid	10.9	10.9	0.0	10.7	10.7	0.0
Subsidized, with Medicaid	61.6	61.6	0.0	65.0	65.0	0.0
Risk scores [c]						
Liu score	6.4 (4.0)	6.3 (4.0)	2.6	6.2 (3.9)	6.3 (4.0)	2.1
van Walraven score	16.6 (9.8)	16.3 (9.7)	3.2	16.0 (9.2)	16.5 (10.0)	4.9

Medication score 1	-6.6 (8.7)	-6.6 (8.6)	2.4	-6.9 (8.6)	-6.4 (8.7)	11.1
Medication score 2	-6.6 (8.9)	-6.6 (8.9)	1.6	-6.7 (8.7)	-6.5 (8.9)	6.9
Medication score 3	8.5 (8.5)	8.5 (8.5)	0.7	8.4 (8.6)	8.6 (8.3)	5.8
Medication score 4	12.2 (8.2)	12.1 (8.2)	1.0	12.0 (7.9)	12.1 (8.2)	0.8
Body mass index [d] (kg / m^2)	27.3 (6.5)	27.4 (6.5)	2.2	27.6 (6.6)	27.4 (6.4)	3.2
Hematocrit [e] (%)	33.6 (3.1)	33.7 (3.0)	2.5	33.9 (3.0)	33.6 (3.0)	9.7
Hospitalization history [d] (days)	7.1 (12.7)	6.9 (12.4)	1.3	6.6 (11.9)	6.6 (13.0)	0.7
Kidney transplant waitlist registration [b] (%)	11.8	10.9	2.8	13.3	15.7	6.7
ESA exposure [e]						
No exposure (%)	7.4	7.9	2.1	7.9	7.9	0.0
Darbepoetin alfa dose [f] (mcg)	786 (778)	832 (824)	5.8	760 (690)	772 (825)	1.6
Epoetin alfa dose [f] (1000s IU)	225 (217)	219 (208)	3.0	214 (196)	231 (229)	8.0
Intravenous VDA exposure [e]						
No exposure (%)	22.5	21.7	1.9	20.3	20.2	0.3
Calcitriol dose [f] (mcg)	36 (25)	34 (26)	10.6	41 (47)	38 (25)	8.0
Doxercalciferol dose [f] (mcg)	130 (83)	133 (81)	4.2	134 (85)	142 (98)	8.3
Paricalcitol dose [f] (mcg)	172 (134)	175 (142)	2.2	173 (155)	165 (128)	5.6
Dialytic modality [b] (%)						
Hemodialysis	96.1	96.4	1.8	97.1	96.6	3.1
Peritoneal dialysis	3.9	3.6	1.8	2.9	3.4	3.1
Dialysis provider [b] (%)						
Fresenius Medical Care	34.8	35.4	1.3	36.6	31.8	10.2
DaVita	27.1	27.3	0.4	29.6	29.4	0.5
Dialysis Clinic, Inc. (DCI)	2.8	3.4	3.7	2.6	1.7	5.9
Small dialysis organization	11.2	10.7	1.5	10.6	12.7	6.4
Independent dialysis provider	15.6	14.7	2.4	14.5	17.8	9.1
Hospital-based dialysis provider	8.4	8.4	0.1	6.1	6.4	1.3
Unknown affiliation	0.3	0.2	2.3	0.0	0.2	NA
Co-incident cardiovascular morbidity [g] (%)						
Myocardial infarction	3.7	3.7	0.0	2.6	4.7	11.5
Stroke	0.4	0.3	0.5	0.1	0.4	6.2
Specialty care during HF hospitalization (%)						
Cardiologist	84.1	84.8	1.9	85.2	83.3	5.3
Nephrologist	86.4	86.5	0.3	86.6	87.8	3.5

Pulmonologist	19.0	18.2	2.2	19.5	20.4	2.2
Procedures during HF hospitalization (%)						
Coronary catheterization	12.8	16.0	9.2	11.1	15.0	11.8
Echocardiogram	30.4	31.9	3.2	33.4	31.3	4.4
Electrocardiogram	76.6	76.6	0.0	75.2	78.5	7.9
Exercise electrocardiography	10.6	11.9	4.0	9.8	10.9	3.9
Myocardial perfusion scintigraphy	7.6	8.9	4.7	6.6	7.5	3.8
Length of stay [g] (days)	4.5 (3.8)	4.6 (3.7)	1.6	4.7 (3.9)	4.9 (4.3)	4.6
Discharge location (%)						
Home, under self-care	81.3	81.7	1.0	82.5	81.1	3.6
Home health agency	18.7	18.3	1.0	17.5	18.9	3.6
Early re-hospitalization [h] (%)	5.5	9.5	15.2	6.2	7.1	3.5
Concomitant exposure [h] (%)						
Beta blocker	16.0	53.3	85.3	18.7	48.1	65.6
Digoxin	1.5	3.4	11.7	1.5	3.0	10.1

Note: For quantities not displayed as percentages, summaries are displayed as mean and standard deviation (in parentheses).

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; ASD, absolute standardized difference; HF, heart failure; ESA, erythropoiesis-stimulating agent; ESRD, end stage renal disease; IU, international units; VDA, vitamin D analogue.

[a] Difference between exposed patients and matched controls, in percentage of 1 standard deviation.

[b] At the start of risk.

[c] During the 12 months before admission for heart failure.

[d] During the 6 months before admission for heart failure.

[e] During the 3 months before admission for heart failure.

[f] Among patients with at least one administration.

[g] During hospitalization for heart failure.

[h] Between discharge and the start of risk.

Table 4-6. Adjusted hazard ratios for ACE-inhibitor exposed patients versus respective matched controls and ARB-exposed patients versus respective matched controls, by follow-up rule

	Intention-to-treat			On-treatment		
	HR	95% CI	*P*	HR	95% CI	*P*
Mortality						
All-cause						
ACE inhibitor	0.90	(0.80.1-00)		0.77	(0.66-0.90)	
ARB	0.83	(0.67-1.01)	0.11	0.73	(0.54-0.99)	0.11
Cardiovascular						
ACE inhibitor	0.94	(0.80-1.10)		0.81	(0.65-1.01)	
ARB	0.82	(0.61-1.10)	0.06	0.77	(0.51-1.16)	0.58
Sudden cardiac death						
ACE inhibitor	0.84	(0.68-1.04)		0.87	(0.64-1.17)	
ARB	0.97	(0.68-1.39)	0.16	0.89	(0.54-1.48)	0.16
Hospitalization						
All-cause						
ACE inhibitor	0.89	(0.86-0.92)		0.88	(0.84-0.92)	
ARB	1.00	(0.94-1.07)	< 0.01	0.98	(0.89-1.07)	< 0.01
Cardiovascular						
ACE inhibitor	0.91	(0.86-0.96)		0.91	(0.84-0.98)	
ARB	1.05	(0.94-1.16)	< 0.01	1.15	(1.00-1.32)	< 0.01
Heart failure						
ACE inhibitor	0.92	(0.84-1.01)		0.96	(0.85-1.08)	
ARB	1.01	(0.86-1.20)	0.03	1.10	(0.89-1.36)	0.12

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CI, confidence interval; HR, hazard ratio.

Table 4-7. Characteristics of candidate controls, matched controls, and exposed patients, among heart failure cases ascertained from principal and secondary diagnoses

	Candidate controls	Matched controls	Exposed patients	ASD [a]
Sample size	16,084	6878	3439	
Age [b] (years)	64.7 (14.3)	63.9 (14.3)	63.9 (14.2)	0.1
Race (%)				
White	54.9	50.5	50.4	0.1
Black	39.9	43.9	43.7	0.4
Native American	1.4	1.7	1.6	0.7
Asian	3.4	3.5	3.8	1.2
Other	0.5	0.5	0.6	1.2
Sex (%)				
Female	48.5	47.1	47.3	0.4
Male	51.5	52.9	52.7	0.4
Primary cause of ESRD (%)				
Diabetes	42.5	41.1	41.0	0.2
Hypertension	31.2	33.0	32.9	0.2
Polycystic kidney disease	9.6	10.4	10.3	0.3
Glomerulonephritis	2.3	2.2	2.3	1.2
Other cause	11.1	10.3	10.2	0.2
Unknown cause	3.4	3.1	3.3	0.9
ESRD duration [b] (years)	5.6 (5.0)	5.2 (4.7)	5.2 (4.8)	0.5
Low-income subsidy reciept [b] (%)				
Not subsidized	29.9	25.2	25.2	0.0
Subsidized, without Medicaid	10.5	10.6	10.6	0.0
Subsidized, with Medicaid	59.7	64.2	64.2	0.0
Risk scores [c]				
Liu score	5.4 (3.6)	4.6 (3.4)	4.6 (3.5)	1.1
van Walraven score	14.4 (9.1)	13.1 (8.7)	13.0 (8.6)	0.6
Medication score 1	-5.5 (8.3)	-7.3 (8.0)	-7.3 (8.0)	0.1

Medication score 2	-5.7 (8.5)	-6.8 (8.4)	-6.9 (8.4)	1.0
Medication score 3	8.7 (8.7)	6.7 (7.6)	6.8 (7.7)	0.9
Medication score 4	11.8 (8.2)	10.4 (7.6)	10.5 (7.6)	0.6
Body mass index [d] (kg / m^2)	28.7 (7.3)	27.7 (6.6)	27.7 (6.6)	0.1
Hematocrit [e] (%)	34.0 (3.0)	33.8 (3.1)	33.9 (3.1)	0.6
Hospitalization history [d] (days)	5.6 (11.6)	4.5 (9.7)	4.5 (9.8)	0.2
Kidney transplant waitlist registration [b] (%)	13.1	13.0	13.1	0.4
ESA exposure [e]				
No exposure (%)	9.2	10.5	10.7	0.5
Darbepoetin alfa dose [f] (mcg)	699 (713)	795 (820)	777 (832)	2.2
Epoetin alfa dose [f] (1000s IU)	218 (222)	216 (216)	212 (212)	2.0
Intravenous VDA exposure [e]				
No exposure (%)	24.3	24.3	24.1	0.3
Calcitriol dose [f] (mcg)	32 (29)	35 (30)	32 (31)	8.7
Doxercalciferol dose [f] (mcg)	132 (90)	136 (93)	137 (88)	0.8
Paricalcitol dose [f] (mcg)	173 (136)	181 (146)	178 (138)	2.0
Dialytic modality [b] (%)				
Hemodialysis	95.6	95.6	95.7	0.4
Peritoneal dialysis	4.4	4.4	4.3	0.4
Dialysis provider [b] (%)				
Fresenius Medical Care	34.2	33.8	34.0	0.5
DaVita	27.4	28.4	28.2	0.3
Dialysis Clinic, Inc. (DCI)	3.6	3.7	3.9	0.7
Small dialysis organization	9.8	9.9	10.2	0.7
Independent dialysis provider	15.3	15.6	15.5	0.3
Hospital-based dialysis provider	9.4	8.2	7.9	1.2
Unknown affiliation	0.2	0.4	0.4	0.2
Co-incident cardiovascular morbidity [g] (%)				
Myocardial infarction	5.2	10.2	12.8	7.9
Stroke	0.6	0.9	1.0	0.9
Specialty care during HF hospitalization (%)				
Cardiologist	68.5	83.4	82.8	1.7
Nephrologist	84.2	85.7	85.8	0.3
Pulmonologist	17.0	19.6	20.1	1.1

Procedures during HF hospitalization (%)				
Coronary catheterization	8.9	18.6	22.1	8.8
Echocardiogram	23.0	32.5	33.2	1.4
Electrocardiogram	67.1	74.1	73.6	1.2
Exercise electrocardiography	5.5	10.1	10.7	2.1
Myocardial perfusion scintigraphy	4.0	7.4	8.2	2.8
Length of stay [g] (days)	5.3 (5.4)	5.6 (5.0)	5.8 (5.1)	2.1
Discharge location (%)				
Home, under self-care	79.0	80.4	80.6	0.6
Home health agency	21.0	19.6	19.4	0.6
Early re-hospitalization [h] (%)		5.8	10.6	17.6
Concomitant exposure [h] (%)				
Beta blocker		19.5	54.4	77.6
Digoxin		1.3	2.8	10.1

Note: For quantities not displayed as percentages, summaries are displayed as mean and standard deviation (in parentheses).

Abbreviations: ASD, absolute standardized difference; HF, heart failure; ESA, erythropoiesis-stimulating agent; ESRD, end stage renal disease; IU, international units; VDA, vitamin D analogue.

[a] Difference between exposed patients and matched controls, in percentage of 1 standard deviation.

[b] At the start of risk.

[c] During the 12 months before admission for heart failure.

[d] During the 6 months before admission for heart failure.

[e] During the 3 months before admission for heart failure.

[f] Among patients with at least one administration.

[g] During hospitalization for heart failure.

[h] Between discharge and the start of risk.

Table 4-8. Adjusted hazard ratios for exposed patients versus matched controls, by follow-up rule, among heart failure cases ascertained from principal and secondary diagnoses

	Intention-to-treat			On-treatment		
	HR	95% CI	*P*	HR	95% CI	*P*
Mortality						
All-cause	0.88	(0.81-0.96)	< 0.01	0.79	(0.70-0.89)	< 0.01
Cardiovascular	0.91	(0.80-1.03)	0.12	0.85	(0.72-1.01)	0.06
Sudden cardiac death	0.93	(0.80-1.09)	0.39	0.91	(0.73-1.14)	0.41
Hospitalization						
All-cause	0.92	(0.88-0.95)	< 0.01	0.92	(0.88-0.96)	< 0.01
Cardiovascular	0.98	(0.92-1.04)	0.46	1.04	(0.98-1.12)	0.19
Heart failure	1.11	(1.01-1.21)	0.02	1.23	(1.11-1.36)	< 0.01
Cardiovascular morbidity						
Myocardial infarction	0.97	(0.83-1.14)	0.69	1.28	(1.05-1.57)	0.01
Stroke	1.02	(0.82-1.28)	0.84	0.98	(0.73-1.31)	0.90
Safety						
Angioedema	1.76	(0.86-3.58)	0.12	2.30	(0.83-6.34)	0.11
Hyperkalemia	0.85	(0.78-0.94)	< 0.01	0.81	(0.73-0.91)	< 0.01

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

Table 4-9. Characteristics of candidate controls, matched controls, and exposed patients, among heart failure cases ascertained from principal diagnoses, but with broad exclusion criteria regarding history of heart failure

	Candidate controls	Matched controls	Exposed patients	ASD [a]
Sample size	6448	3548	1774	
Age [b] (years)	65.5 (14.2)	64.9 (14.2)	64.9 (14.1)	0.2
Race (%)				
White	55.9	50.9	50.8	0.3
Black	38.9	43.7	43.8	0.3
Native American	1.0	1.1	1.2	0.8
Asian	3.7	3.9	3.8	0.3
Other	0.4	0.4	0.4	0.4
Sex (%)				
Female	49.5	49.1	48.7	0.7
Male	50.5	50.9	51.3	0.7
Primary cause of ESRD (%)				
Diabetes	41.7	41.0	39.9	2.3
Hypertension	32.2	33.3	33.8	0.9
Polycystic kidney disease	10.0	10.1	10.7	1.9
Glomerulonephritis	2.2	2.0	2.0	0.2
Other cause	10.5	10.2	10.2	0.3
Unknown cause	3.3	3.4	3.6	1.2
ESRD duration [b] (years)	5.4 (4.6)	5.1 (4.5)	5.1 (4.4)	0.6
Low-income subsidy reciept [b] (%)				
Not subsidized	30.5	26.6	26.6	0.0
Subsidized, without Medicaid	10.4	11.2	11.2	0.0
Subsidized, with Medicaid	59.1	62.3	62.3	0.0
Risk scores [c]				
Liu score	6.4 (4.0)	5.6 (3.8)	5.5 (3.8)	2.7
van Walraven score	16.5 (9.8)	15.0 (9.4)	14.8 (9.4)	1.9
Medication score 1	-5.8 (8.5)	-7.3 (8.5)	-7.3 (8.4)	0.8

Medication score 2	-6.1 (8.8)	-7.1 (8.8)	-7.1 (8.8)	0.1
Medication score 3	9.1 (9.1)	7.6 (8.2)	7.6 (8.2)	0.8
Medication score 4	12.4 (18.5)	11.3 (8.0)	11.3 (7.9)	0.8
Body mass index [d] (kg / m^2)	28.2 (7.0)	27.5 (6.7)	27.5 (6.5)	0.5
Hematocrit [e] (%)	33.7 (3.0)	33.6 (3.0)	33.6 (2.9)	0.3
Hospitalization history [d] (days)	7.2 (12.7)	6.3 (12.1)	6.0 (12.1)	2.4
Kidney transplant waitlist registration [b] (%)	12.7	13.1	13.3	0.5
ESA exposure [e]				
No exposure (%)	6.9	7.2	7.8	2.3
Darbepoetin alfa dose [f] (mcg)	743 (697)	778 (729)	835 (839)	7.3
Epoetin alfa dose [f] (1000s IU)	234 (225)	225 (211)	222 (208)	1.3
Intravenous VDA exposure [e]				
No exposure (%)	21.5	20.8	21.0	0.4
Calcitriol dose [f] (mcg)	31 (28)	36 (29)	33 (25)	11.7
Doxercalciferol dose [f] (mcg)	130 (87)	136 (91)	139 (88)	4.1
Paricalcitol dose [f] (mcg)	169 (136)	177 (144)	176 (142)	0.2
Dialytic modality [b] (%)				
Hemodialysis	97.0	96.6	96.3	1.5
Peritoneal dialysis	3.0	3.4	3.7	1.5
Dialysis provider [b] (%)				
Fresenius Medical Care	35.6	34.9	34.0	1.8
DaVita	28.3	26.7	27.3	1.5
Dialysis Clinic, Inc. (DCI)	3.5	3.1	3.2	0.5
Small dialysis organization	9.9	11.6	11.8	0.4
Independent dialysis provider	14.3	16.0	15.7	1.0
Hospital-based dialysis provider	8.2	7.5	7.8	1.2
Unknown affiliation	0.1	0.2	0.2	0.6
Co-incident cardiovascular morbidity [g] (%)				
Myocardial infarction	2.3	3.4	4.1	3.4
Stroke	0.1	0.2	0.3	2.7
Specialty care during HF hospitalization (%)				
Cardiologist	75.0	86.0	86.0	0.0
Nephrologist	83.4	87.3	86.0	3.9
Pulmonologist	18.0	18.9	18.7	0.6

Procedures during HF hospitalization (%)				
Coronary catheterization	7.3	12.7	16.9	11.8
Echocardiogram	24.0	30.6	32.0	2.9
Electrocardiogram	74.5	76.3	76.8	1.3
Exercise electrocardiography	6.8	10.6	12.9	6.9
Myocardial perfusion scintigraphy	4.6	7.4	9.6	8.0
Length of stay [g] (days)	4.2 (3.9)	4.5 (3.7)	4.6 (3.7)	1.6
Discharge location (%)				
Home, under self-care	81.2	83.0	83.3	0.9
Home health agency	18.8	17.0	16.7	0.9
Early re-hospitalization [h] (%)		5.9	9.4	13.2
Concomitant exposure [h] (%)				
Beta blocker		16.3	52.5	82.3
Digoxin		1.5	3.0	10.7

Note: For quantities not displayed as percentages, summaries are displayed as mean and standard deviation (in parentheses).

Abbreviations: ASD, absolute standardized difference; HF, heart failure; ESA, erythropoiesis-stimulating agent; ESRD, end stage renal disease; IU, international units; VDA, vitamin D analogue.

[a] Difference between exposed patients and matched controls, in percentage of 1 standard deviation.

[b] At the start of risk.

[c] During the 12 months before admission for heart failure.

[d] During the 6 months before admission for heart failure.

[e] During the 3 months before admission for heart failure.

[f] Among patients with at least one administration.

[g] During hospitalization for heart failure.

[h] Between discharge and the start of risk.

Table 4-10. Adjusted hazard ratios for exposed patients versus matched controls, by follow-up rule, among heart failure cases ascertained from principal diagnoses, but with broad exclusion criteria regarding history of heart failure

	Intention-to-treat			On-treatment		
	HR	95% CI	*P*	HR	95% CI	*P*
Mortality						
All-cause	0.79	(0.70-0.89)	< 0.01	0.71	(0.60-0.84)	< 0.01
Cardiovascular	0.82	(0.69-0.98)	0.03	0.78	(0.61-1.00)	0.05
Sudden cardiac death	0.77	(0.61-0.97)	0.03	0.80	(0.57-1.11)	0.18
Hospitalization						
All-cause	0.87	(0.82-0.93)	< 0.01	0.85	(0.79-0.91)	< 0.01
Cardiovascular	0.92	(0.85-0.99)	0.03	1.01	(0.92-1.10)	0.90
Heart failure	0.96	(0.86-1.07)	0.43	1.05	(0.93-1.18)	0.46
Cardiovascular morbidity						
Myocardial infarction	1.14	(0.92-1.42)	0.23	1.24	(0.93-1.65)	0.14
Stroke	1.14	(0.82-1.59)	0.44	1.04	(0.69-1.56)	0.87
Safety						
Angioedema	1.65	(0.71-3.84)	0.24	2.09	(0.51-8.53)	0.30
Hyperkalemia	0.85	(0.74-0.98)	0.02	0.75	(0.65-0.87)	< 0.01

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

Figure 4-1A. Cumulative incidence of death for exposed patients and matched controls in intention-to-treat follow-up

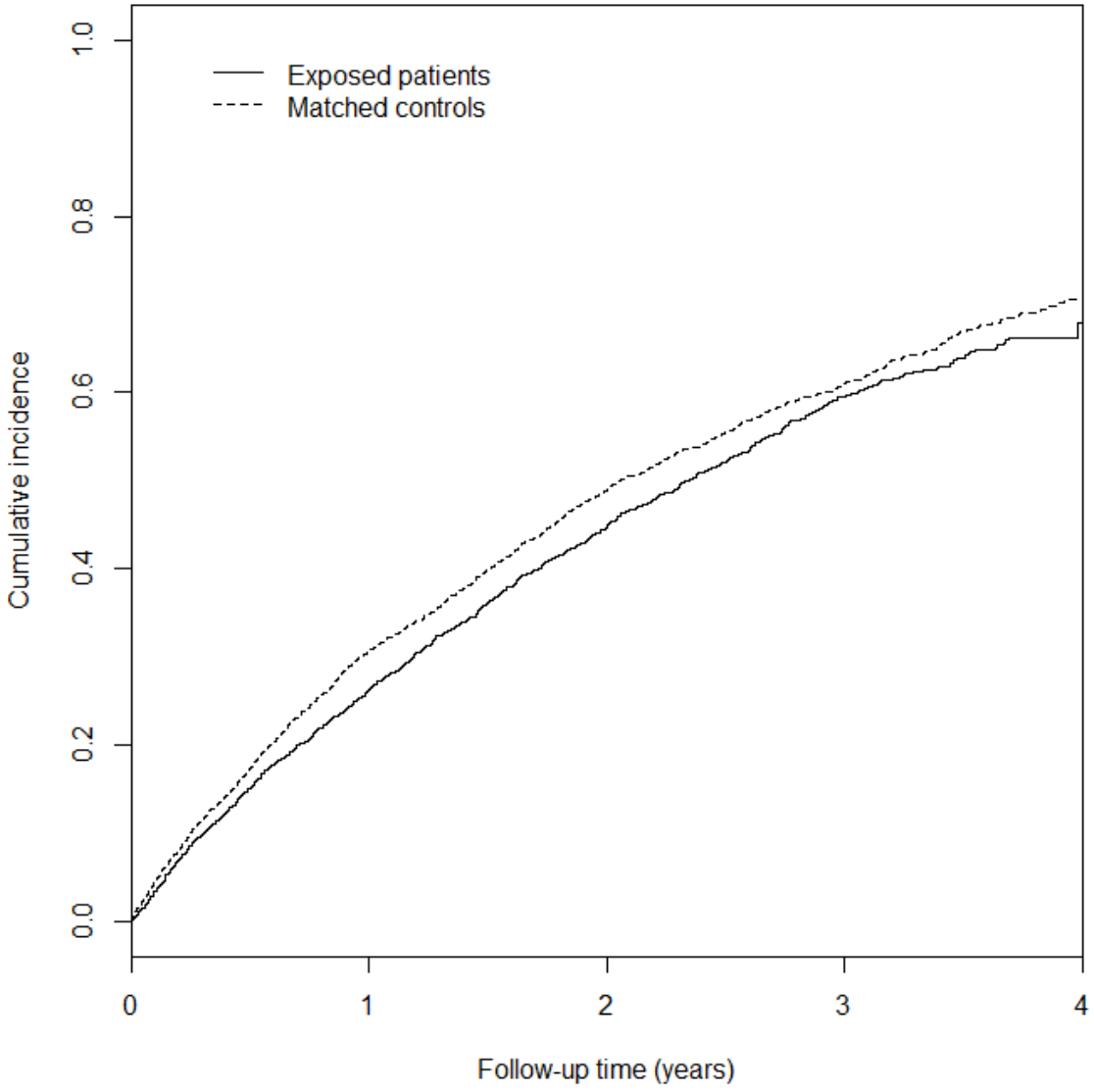


Figure 4-1B. Cumulative incidence of death for exposed patients and matched controls in on-treatment follow-up

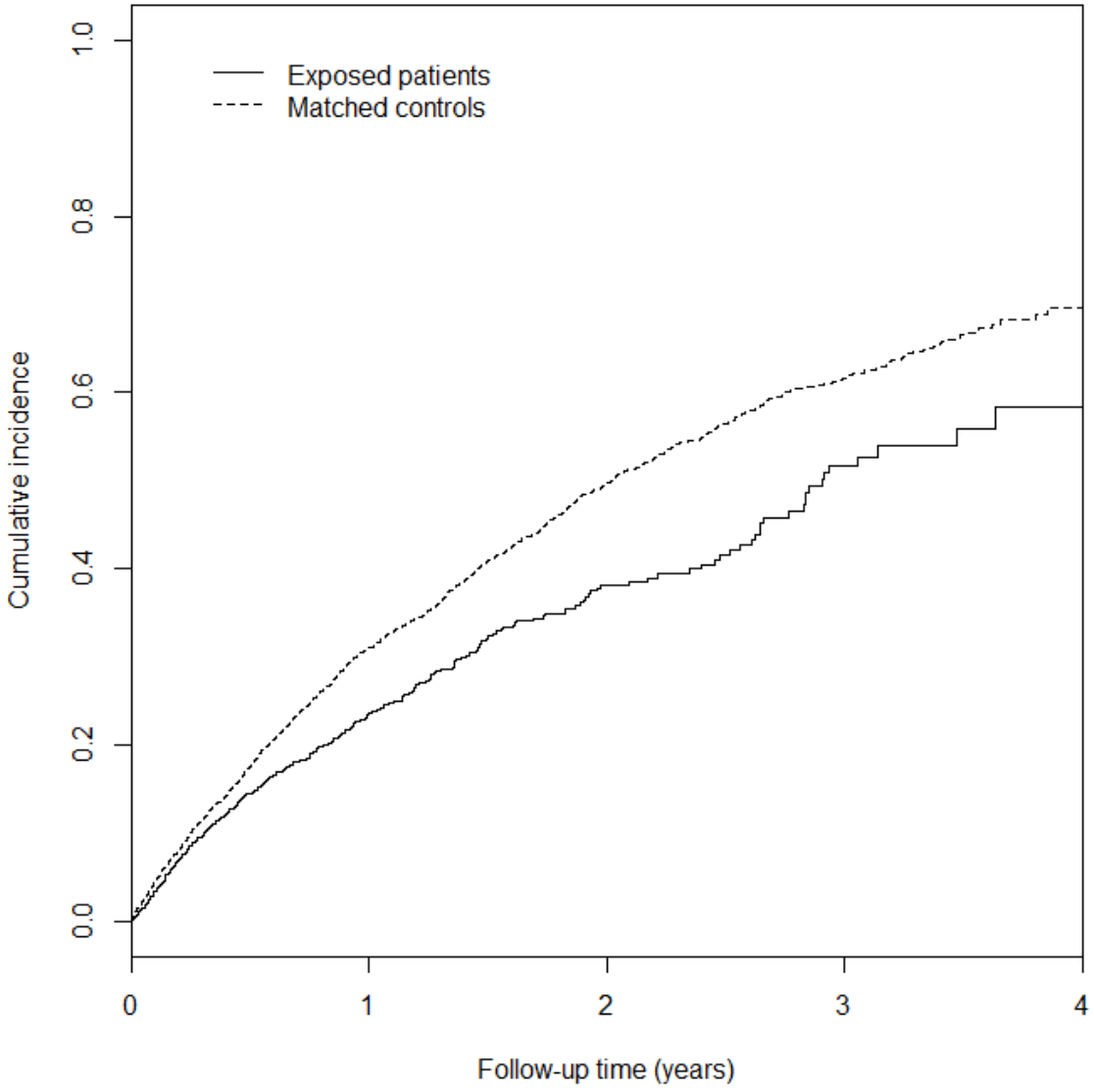


Figure 4-2A. Cumulative incidence of cardiovascular death for exposed patients and matched controls in intention-to-treat follow-up

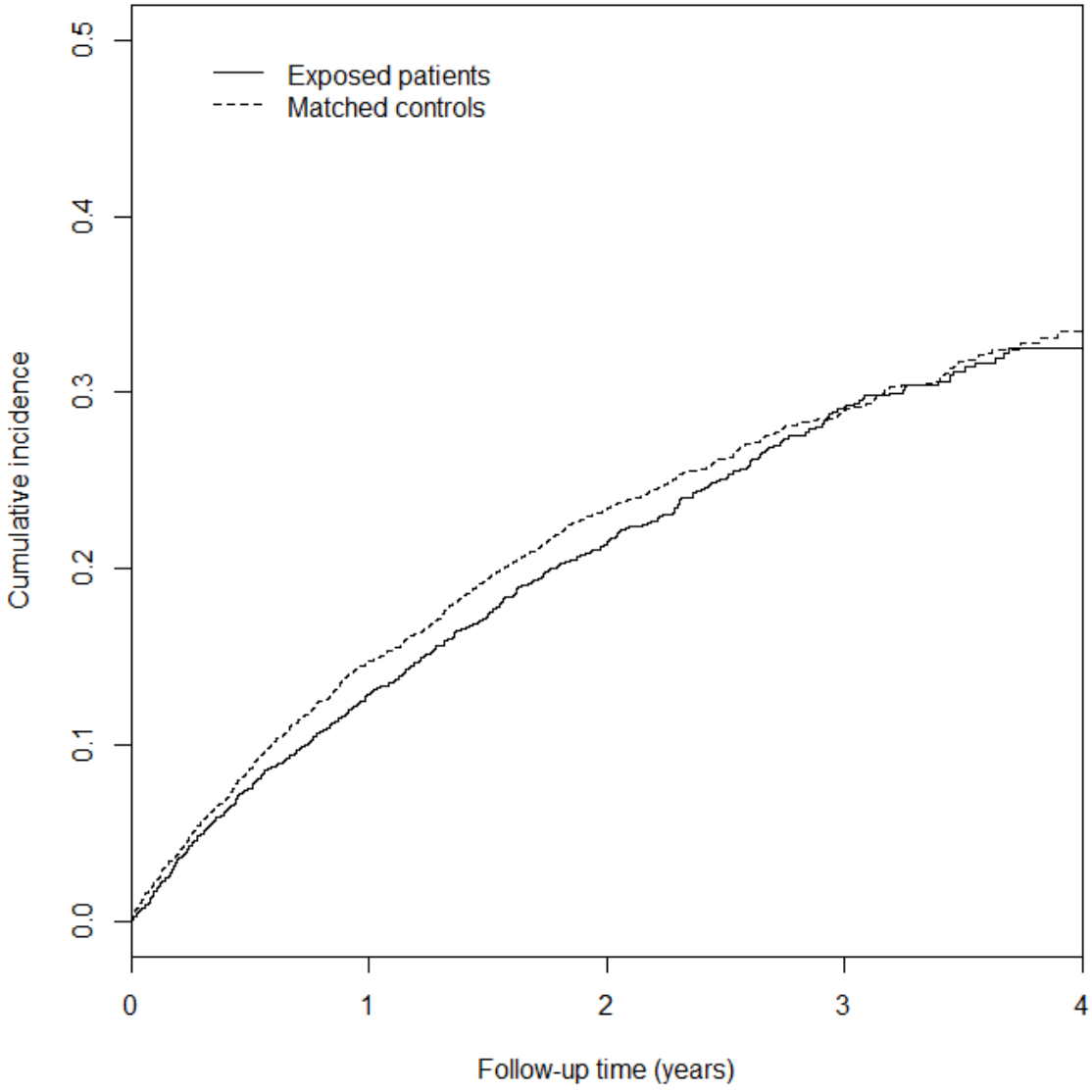


Figure 4-2B. Cumulative incidence of cardiovascular death for exposed patients and matched controls in on-treatment follow-up

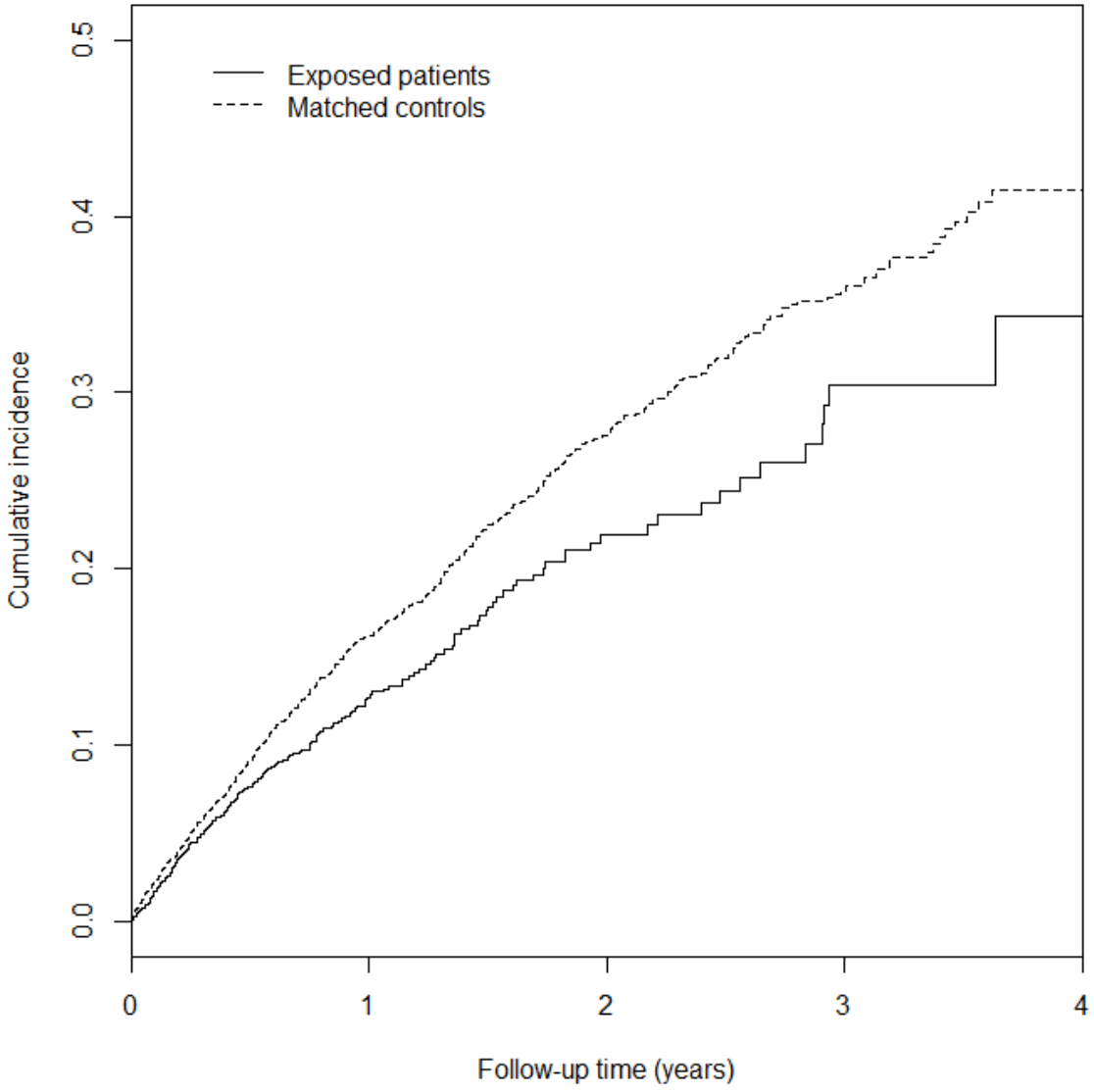


Figure 4-3A. Cumulative incidence of sudden cardiac death for exposed patients and matched controls in intention-to-treat follow-up

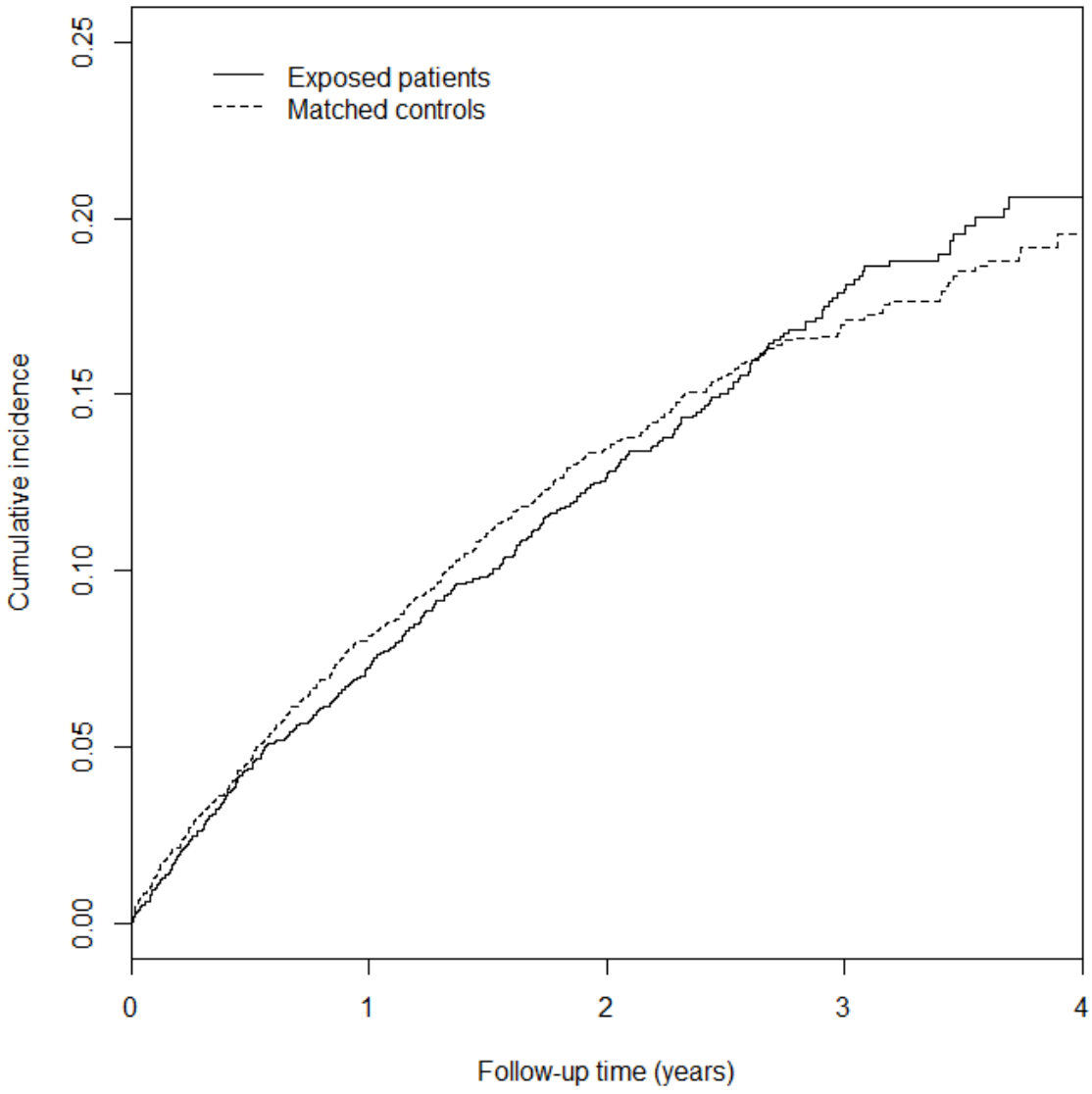


Figure 4-3B. Cumulative incidence of sudden cardiac death for exposed patients and matched controls in on-treatment follow-up

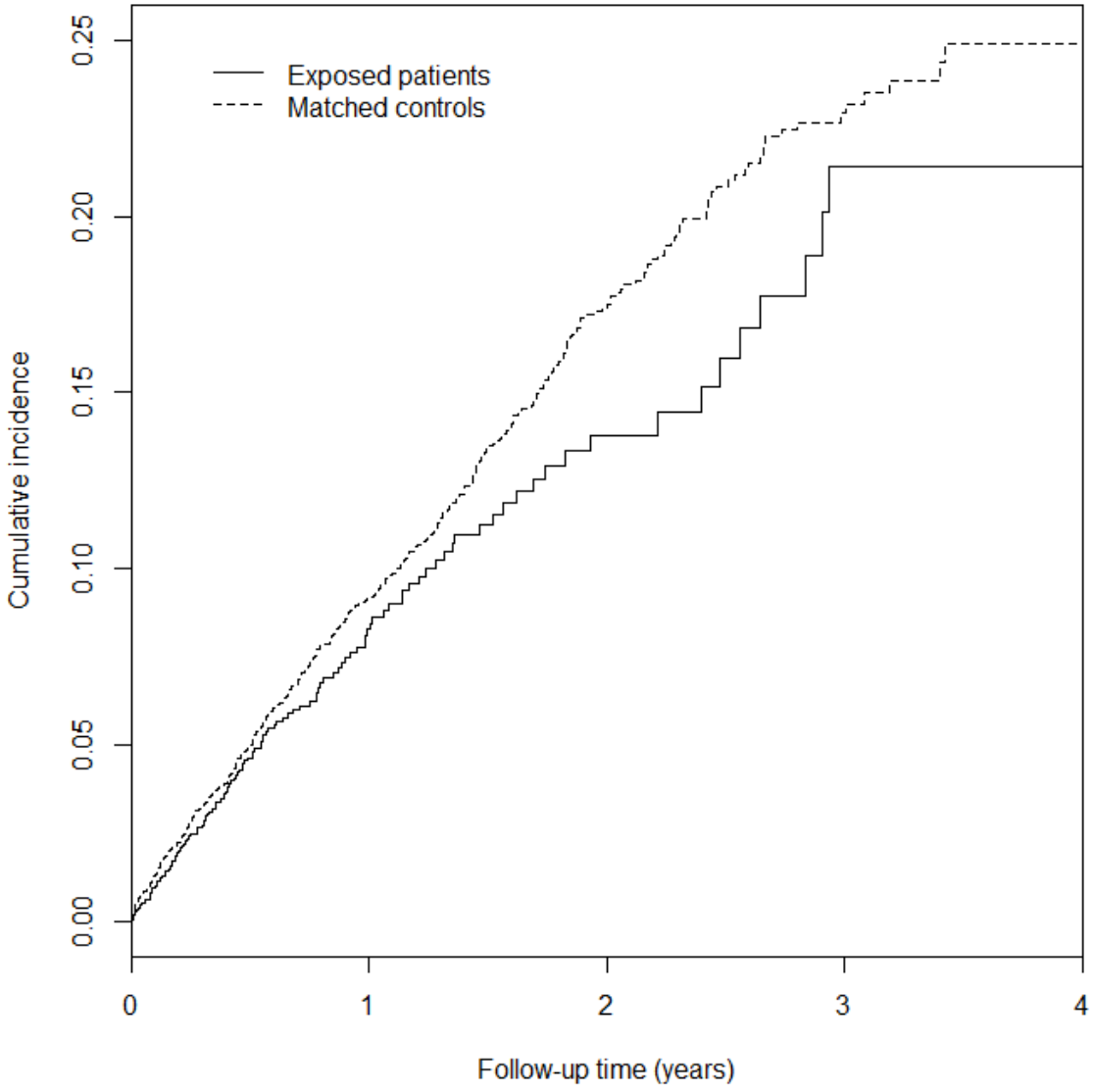
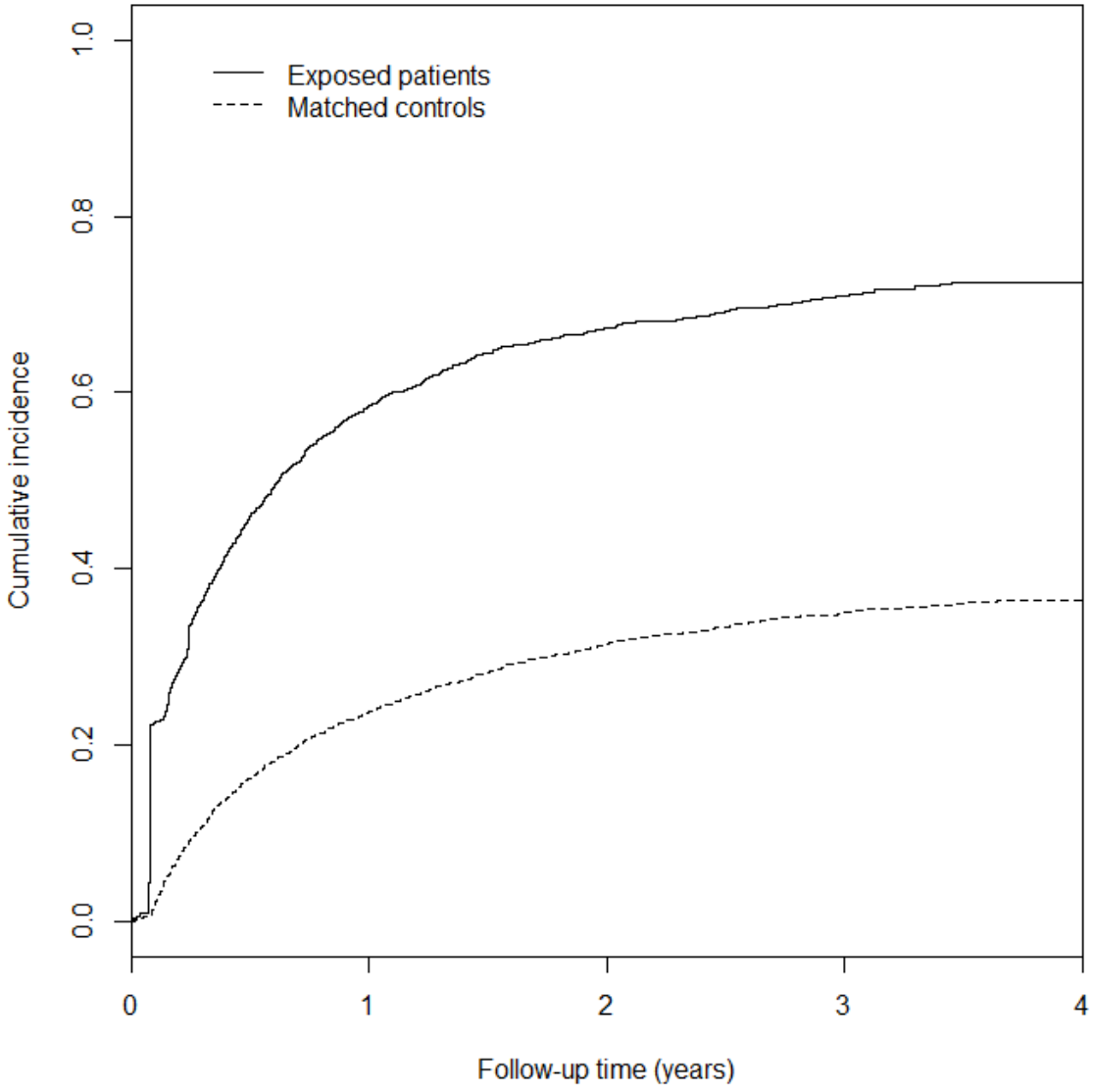


Figure 4-4. Cumulative incidence of change in exposure status for exposed patients and matched controls



Chapter 5

Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Hemodialysis Patients with Heart Failure

Abstract

Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) are commonly used to treat heart failure (HF), but few studies have compared clinical outcomes across agents in these classes. In dialysis patients, differences in the properties of these agents may have significant consequences. We used data from the United States Renal Data System to assess the relative hazards of death and hospitalization associated with use of benazepril, enalapril, lisinopril, ramipril, losartan, and valsartan in dialysis patients that had been discharged after hospitalization principally for HF. Discharges were ascertained from Medicare Part A claims between January 1, 2007, and December 31, 2011. ACE inhibitor and ARB exposure was ascertained from Part D claims during the 1 month following discharge. We fit adjusted Cox and Anderson-Gill models of death and hospitalization, respectively, and used nonparametric bootstrapping to compare and rank hazards associated with agents. There were 3854, 1208, 685, 624, and 457 users of lisinopril, valsartan, enalapril, losartan, benazepril, and ramipril, respectively. In intention-to-treat analysis, relative to lisinopril, mortality hazard ratios (HRs) were 0.84 (95% confidence interval, 0.75-0.94) for valsartan, 0.89 (0.77-1.01) for enalapril, 0.97 (0.85-1.09) for losartan, 0.96 (0.82-1.13) for benazepril, and 1.15 (0.96-1.36) for ramipril. The bootstrapped probability that valsartan was associated with lowest risk was 71.3%. The hospitalization HR for valsartan versus lisinopril was 0.93 (0.87-0.99). After 3 months of treatment, 56.4% of lisinopril users received 20 or 40

mg/day, whereas 80.6% of valsartan users received 160 or 320 mg/day. However, after 12 months, more than 50% of users in each group had experienced an interruption in treatment for > 1 month. In summary, these data suggest that the choice of a renin-angiotensin system inhibitor for HF in dialysis patient may be important; lisinopril may not be the ideal agent. Randomized trials are needed to confirm findings.

Introduction

Pharmacologic inhibition of the renin-angiotensin system (RAS) is recommended for the treatment of heart failure (HF) with reduced ejection fraction (EF); for the treatment of HF with preserved EF, inhibition of the RAS may be effective, but evidence is equivocal.[86-87] Inhibition of the RAS may be achieved with angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs). Today, there are ten orally administered ACE inhibitors and eight ARBs available for prescription in the US. Meta-analysis of trials that enrolled patients with HF indicates that ARBs are superior to placebo in reducing risks of death and HF hospitalization, but non-inferior to ACE inhibitors.[88] Whether class effects exist among ACE inhibitors and ARBs is unclear.[89] Not all agents were tested in randomized clinical trials of patients with HF. Moreover, differences in absorption, distribution, metabolism, and excretion may engender differences in clinical efficacy. For patients without renal function, the selection of an ACE inhibitor or ARB may be especially important. The ratio of renal to hepatic elimination varies widely across ACE inhibitors and ARBs.[90] Potentially more importantly, all ACE inhibitors except fosinopril are cleared by dialysis, whereas ARBs are not cleared.[91] Studies are clearly needed to guide physicians in selection of these agents.

In this study, we used United States Renal Data System (USRDS) data to compare risks of mortality and hospitalization among four ACE inhibitors (benazepril, enalapril, fosinopril, lisinopril) and two ARBs (losartan, valsartan) in dialysis patients who were discharged from the hospital with a principal diagnosis of HF. Data regarding medication exposure were ascertained from Medicare Part D claims. We assessed all-cause death,

cardiovascular death, sudden cardiac death, all-cause hospitalization, cardiovascular hospitalization, and HF hospitalization.

Methods

Protection of Human Subjects

We analyzed USRDS data that were obtained by a Data Use Agreement with the National Institute of Diabetes and Digestive and Kidney Diseases. The study was reviewed by the Human Subjects Research Committee at Hennepin County Medical Center (Minneapolis, Minnesota).

Study Cohort

The source cohort included prevalent and incident dialysis patients. For the former, we retained patients with receipt of dialysis on December 31, 2007 (*i.e.*, index date); uninterrupted receipt of one dialytic modality (*i.e.*, either hemodialysis or peritoneal dialysis) during 2007; date of initiation of renal replacement therapy no later than October 31, 2006; age between 20 and 100 years on the index date; and uninterrupted enrollment in Medicare Parts A and B during the 12-month interval immediately preceding the index date. For the latter, we retained patients with date of initiation of dialysis (*i.e.*, index date) between January 1, 2007, and December 31, 2009; age between 20 and 100 years on the index date; and uninterrupted enrollment in Medicare Parts A and B during the 12-month interval immediately preceding the index date. For both groups, we required non-missing data regarding race, sex, primary cause of ESRD, and ESRD Network of residence on the index date. We excluded patients with a hospitalization for HF (*International Classification of Diseases, Ninth Revision, Clinical*

Modification [ICD-9-CM] diagnosis code 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, or 428.*x* as principal diagnosis[92]) during the 12-month interval immediately preceding the index date.

We followed each patient from the index date to the earliest of death, kidney transplant, interruption of enrollment in Medicare Parts A and B, or December 31, 2011. During follow-up, we identified the first hospitalization for HF. We retained hospitalized patients with Medicare Part D enrollment during the 12-month interval immediately preceding the date of admission, in receipt of hemodialysis after admission, and with discharge to home, under either self-care or the supervision of a home health agency.

Patient Characteristics

For each patient, we ascertained age, race, sex, primary cause of ESRD, ESRD duration, ESRD Network of residence, socioeconomic status, comorbidity scores, body mass index (BMI), hematocrit, recent hospitalization, kidney transplant wait-list status, erythropoiesis-stimulating agent (ESA) and intravenous vitamin D analogue (VDA) exposure, dialytic modality, dialysis provider, HF hospitalization factors (co-incident myocardial infarction and stroke, physician specialty care, diagnostic procedures, and length of stay), and discharge location. The risk scores comprised 2 comorbidity scores and 4 medication scores. For comorbidity, we used the Liu score and the van Walraven score derived from Elixhauser comorbid conditions.[93-94] In each score, we declared a condition to be present if we identified at $\geq$ 1 inpatient facility, skilled nursing facility, or home health agency claim or $\geq$ 2 outpatient facility or physician claims with qualifying ICD-9-CM diagnosis codes, as defined by Quan *et al*, during the 12 months preceding admission.[95-96] For medication, we used scores derived from dispensed medications

during the 12 months preceding admission.[97] BMI and hematocrit were calculated from the means of measurements on outpatient dialysis and ESA claims, respectively, during the 6 months preceding admission. Hospitalization history was summarized by cumulative hospitalized days during the 6 months preceding admission, whereas ESA and intravenous VDA exposure were summarized by cumulative doses during the 3 months preceding admission. Dialytic modality and dialysis provider were identified on the day before admission. During HF hospitalization, myocardial infarction was identified from ICD-9-CM diagnosis codes 410.*x*0 and 410.*x*1;[98] stroke was identified from codes 430.*x*, 431.*x*, 434.*x*, and 436.*x*.[99] Specialty care was identified from physician claims concurrent with hospitalization; diagnostic procedures were identified from both ICD-9-CM procedure codes on inpatient facility claims and *Current Procedural Terminology* (CPT) codes on physician claims concurrent with hospitalization.

Exposure

From Part D claims in the 1 month following discharge, we identified dispensed ACE inhibitors and ARBs, according to the National Drug Code and the associated Generic Product Identifier (GPI) code in the Medi-Span Master Drug Database (Indianapolis, IN). We included combination products with an ACE inhibitor or ARB. We retained patients who were dispensed only one ACE inhibitor or ARB in the month. In consideration of statistical power, we retained only patients who were dispensed benazepril, enalapril, lisinopril, ramipril, losartan, or valsartan. The history and properties of these agents are described in Appendix 2.

We set the start of risk at the date of first dispensation. Between discharge and the start of risk, we identified incidence of rehospitalization and dispensation of beta blockers

and digoxin. We also identified dispensation of RAS inhibitors during the 3 months preceding admission.

Regarding the RAS inhibitor at the start of risk, we calculated prescribed dose per day from the quotient of pill count and days supplied, given the dose per pill indicated by the NDC. We updated prescribed dose per day on the date of each subsequent fill.

Outcomes

We followed all patients from the start of risk to the earliest of death; kidney transplant; interruption of enrollment Medicare in Parts A, B, and D; or December 31, 2011. We identified the incidence of death and hospitalization. We also measured proportion of days covered (PDC) by supply of the initial RAS inhibitor.[100]

Statistical Analysis

We calculated statistical summaries of measured factors in each treatment group and also estimated absolute standardized differences between lisinopril users and valsartan users.[101] We used intention-to-treat (ITT) and on-treatment (OT) rules during follow-up. For the ITT rule, we followed patients from the start of risk to the earliest of death; kidney transplant; interruption of enrollment Medicare in Parts A, B, and D; or December 31, 2011. For the OT rule, we added interruption of treatment with initial RAS inhibitor to the list of dates on which follow-up may end. Specifically, interruption of treatment was defined at the end of the first 1-month interval without supply of the initial RAS inhibitor or 1 month after first dispensation of an alternative RAS inhibitor.

For mortality, we used Kaplan-Meier analysis to estimate survival in treatment groups. To compare survival in these groups, we used Cox proportional hazards regression to estimate relative hazards. The model was adjusted for all patient

characteristics, as well as recent history of dispensation of RAS inhibitors, incidence of rehospitalization between discharge and start of risk, and concomitant dispensation of beta blockers and digoxin. Continuous covariates, except for length of stay, were parameterized with linear monomials; length of stay was parameterized with a quadratic polynomial. For hospitalization, we used Andersen-Gill regression to estimate relative hazards of admission. The model was adjusted for the same factors as in the model for mortality. For both regression models, we used nonparametric bootstrapping with 2000 iterations to estimate model parameters and associated 95% confidence intervals. Furthermore, we derived empirical distributions of the ranks of relative hazards associated with treatment groups.

Regarding exposure during OT follow-up, we calculated the distribution of prescribed dose per day at the start of risk and at 3, 6, 9, and 12 months thereafter. We also calculated the cumulative incidence of RAS inhibitor interruption and treatment group crossover (to another RAS inhibitor), with death as a competing risk. Finally, we used bootstrapping to estimate mean PDC during OT follow-up and 2 variations thereon, with interruptions of treatment defined at the end of the first *k*-month interval without supply of the initial RAS inhibitor or *k* months after first dispensation of an alternative RAS inhibitor ($k = 2, 3$).

All analyses were conducted in SAS, version 9.2 (Cary, North Carolina), except for the exposure status crossover analysis, which was conducted in R, version 3.1.2 (Vienna, Austria).

Results

We identified 7132 hospitalized cases of HF. In the 1 month following discharge, 3854 (54.0%) patients were dispensed lisinopril, 1208 (16.9%) valsartan, 685 (9.6%) enalapril, 624 (8.7%) losartan, 457 (6.4%) benazepril, and 304 (4.3%) ramipril. The characteristics of patients are displayed in Table 5-1, with stratification by agent. Age was highest in ramipril users (mean, 66.9 years) and lowest in benazepril users (63.8 years). Whites were relatively more likely to use ramipril, while Asians were relatively more likely to use losartan or valsartan. Females were also relatively more likely to use losartan or valsartan. Mean comorbidity scores were similar across agents, although mean hospitalized days, both during the 6 months before HF hospitalization and during the HF hospitalization itself, suggested that enalapril and ramipril users were less healthy than other users. During the 3 months before HF hospitalization, use of RAS inhibitors was highest in valsartan (82.2%), benazepril (79.7%), and losartan (79.3%) users; intermediate in enalapril (71.1%) users; and lowest in lisinopril (66.4%) and ramipril (65.5%) users. Prevalence of early re-hospitalization and dispensation of beta blockers was similar across agents. Between lisinopril and valsartan users specifically, several substantial differences (absolute standardized difference > 10%) in characteristics were apparent. Asian race, female sex, and diabetes as the primary cause of ESRD were more likely in valsartan users. Valsartan users were more likely to be subsidized and dually enrolled in Medicare and Medicaid than lisinopril users.

Histories of daily dose distributions of ACE inhibitors and ARBs are displayed in Table 2. At the start of risk, the most common doses were 40 mg (39.8%) of benazepril, 40 mg (27.4%) of enalapril, 40 mg (30.4%) of lisinopril, 10 mg (36.8%) of ramipril, 100

mg (57.7%) of losartan, and 320 mg (49.8%) of valsartan. During OT follow-up, dose distributions shifted in the positive direction. However, the most common doses remained the same, with the exception of enalapril: at 3 months and thereafter, the most common daily dose of enalapril was 80 mg.

Event counts and crude event rates are displayed in Table 5-3. In ITT follow-up, patients accumulated 11,232 patient-years of follow-up. Mean follow-up per patient ranged from 1.51 years in ramipril users to 1.68 years in enalapril users. For mortality, crude rates ranged from 24 deaths per 100 patient-years for valsartan to 35 deaths per 100 patient-years for ramipril; the crude rate for lisinopril was intermediate (29 deaths per 100 patient-years). For hospitalization, crude rates ranged from 295 admissions per 100 patient-years for ramipril to 321 admissions per 100 patient-years for lisinopril. In OT follow-up, patients accumulated 4379 patient-years of follow-up. Mean follow-up per patient ranged from 0.57 years in ramipril users to 0.67 years in valsartan users. Mortality rates ranged from 17 deaths per 100 patient-years for losartan to 31 deaths per 100 patient-years for ramipril; the rate for lisinopril was again intermediate (24 deaths per 100 patient-years). Hospitalization rates ranged from 280 admissions per 100 patient-years for valsartan to 305 admissions per 100 patient-years for lisinopril.

Estimates of survival are displayed are displayed in Figures 5-1A and 5-1B. In ITT analysis, 1-year survival estimates were 79.3% for valsartan, 77.9% for enalapril, 77.2% for losartan, 74.6% for lisinopril, 74.5% for benazepril, and 68.7% for ramipril (Figure 5-1A). After 2 years, survival remained highest for valsartan and lowest for ramipril. In contrast, 1-year survival estimates by OT analysis were 84.9% for losartan,

82.2% for valsartan, 81.7% for enalapril, 80.9% for benazepril, 78.9% for lisinopril, and 76.8% for ramipril.

Adjusted hazard ratios (HRs) of death for pairwise comparisons of agents are displayed in Table 5-4. In ITT analysis, relative to lisinopril, adjusted HRs were 0.96 for benazepril, 0.89 for enalapril, 1.15 for ramipril, 0.97 for losartan, and 0.84 for valsartan; the contrast of valsartan to lisinopril was statistically significant ($P < 0.05$). Adjusted HRs for valsartan versus all other agents were less than 1, while HRs for ramipril versus all other agents were greater than 1. In OT analysis, relative to lisinopril, adjusted HRs were 0.90 for benazepril, 0.92 for enalapril, 1.19 for ramipril, 0.76 for losartan, and 0.78 for valsartan; the contrasts of both losartan and valsartan to lisinopril were statistically significant ($P < 0.05$). Adjusted HRs for ramipril versus all other agents were greater than 1. Meanwhile, adjusted HRs for losartan versus all other agents were less than 1, although the HR of losartan versus valsartan was only 0.97 (95% confidence interval, 0.72-1.29). Bootstrapped probabilities of the ranks of adjusted relative hazards associated with the agents are displayed in Figures 5-2A and 5-2B. In ITT analysis, the estimated probability that valsartan was associated with lowest risk was 71.3%, whereas the probability that enalapril was associated with lowest risk was 22.4% (Figure 5-2A). The probability that lisinopril was associated with lowest risk was 0%. Meanwhile, the probability that ramipril was associated with highest risk was 89.6%. In OT analysis, the probability that either losartan or valsartan was associated with lowest risk was 84.3% (Figure 5-2B).

Adjusted HRs of hospitalization for pairwise comparisons of agents are displayed in Table 5-5. In ITT analysis, relative to lisinopril, adjusted HRs were 1.02 for

benazepril, 0.97 for enalapril, 0.94 for ramipril, 1.03 for losartan, and 0.93 for valsartan; the contrast of valsartan to lisinopril was statistically significant ($P < 0.05$). Adjusted HRs for valsartan versus all other agents were less than 1. In OT analysis, contrasts were generally weak in magnitude. HRs for losartan versus all other agents were greater than 1, but HRs for valsartan versus all other agents were less than 1. Bootstrapped probabilities of the ranks of adjusted relative hazards associated with the agents are displayed in Figures 5-2C and 5-2D. In ITT analysis, the estimated probability that valsartan was associated with lowest risk was 52.7% (Figure 5-2C). The probability that lisinopril was associated with lowest risk was 0.1%. In OT analysis, the probability that valsartan was associated with lowest risk was 39.9%, whereas the probability that lisinopril was associated with lowest risk was 0.3% (Figure 5-2D).

The cumulative incidence of RAS inhibitor interruption is displayed in Figure 5-3. After 1 month, the incidence of interruption was 23.4% for ramipril, 22.4% for enalapril, 20.6% for lisinopril, 17.9% for each of losartan and valsartan, and 16.4% for benazepril. After 12 months, the incidence of interruption was 63.2% for ramipril, 63.0% for enalapril, 61.0% for lisinopril, 58.6% for losartan, 56.5% for valsartan, and 55.2% for benazepril. The cumulative incidence of treatment group crossover is displayed in Figure 5-4. After 12 months, the incidence of crossover was 11.2% for benazepril, 7.6% for enalapril, 7.2% for valsartan, 6.1% for losartan, 5.0% for lisinopril, and 4.8% for ramipril. Thus, after 12 months, the combined incidence of interruption or crossover was highest for enalapril (70.8%) and lowest for valsartan (63.8%). Finally, mean PDC is displayed in Table 5-6. Regardless of follow-up rule, PDC was similar across agents.

Discussion

By American Heart Association guidelines, ACE inhibitors are recommended in patients with heart failure and reduced EF, whereas ARBs are recommended in the subset of patients who are ACE inhibitor-intolerant.[86] The guidelines offer no recommendations regarding the selection of individual ACE inhibitors or ARBs, and few agents have ever been evaluated in randomized clinical trials of patients with heart failure, particularly in absence of myocardial infarction. However, there are several pharmacokinetic differences among the agents and the effects of these differences may be magnified in patients with little or no kidney function. In this study, we assessed comparative effectiveness of 6 agents that were dispensed to hemodialysis patients after discharge from hospitalization principally for heart failure: benazepril, enalapril, lisinopril, ramipril, losartan, and valsartan. We found that lisinopril was the dominant agent in this setting. However, with respect to risks of death and hospitalization, we found little evidence to support its preferential use. Instead, estimated probabilities that valsartan was associated with lowest risks of death and hospitalization were 71% and 53%, respectively, in ITT analysis.

The pharmacology of ACE inhibitors and ARBs is clearly different. ACE inhibitors block the catalytic activity of angiotensin-converting enzyme, thus inhibiting conversion of angiotensin I to angiotensin II and breakdown of bradykinin.[102] On the other hand, ARBs antagonize the type I angiotensin II receptor in blood vessels and cardiac tissue, but do not increase the concentration of bradykinin.[91] Because of different effects on bradykinin, ARBs are less likely to induce cough than ACE inhibitors and thus may be better tolerated.[103] In this study, we found that the combined incidence of interruption and change in treatment was lowest for valsartan. Within subclasses, there

are subtle differences among agents. Among ACE inhibitors in this study, lisinopril is the only agent that is not a prodrug that requires metabolism in the liver; this may be an important feature in hemodialysis patients with not only heart failure, but also fluid overload (*e.g.*, between dialysis sessions) and resultant hepatic congestion.[104] However, we found little evidence that risks of death and hospitalization were substantially lower for lisinopril versus each of benazepril and enalapril. Typical dosing schedules may differ, as a function of half-lives. Both lisinopril and ramipril are typically taken once per day, whereas enalapril is taken twice per day. For dialysis patients, in whom polypharmacy is common, adherence to once-daily doses may be superior.[105] All of the ACE inhibitors in this study are cleared by hemodialysis. (Technically, benazepril is cleared by hemodialysis, but its active metabolite, benazeprilat, is not.) In contrast, neither of the ARBs are cleared. This may be important; Weir *et al* reported that high-dialyzability versus low-dialyzability beta blockers were associated with excess risk of death.[106] Among ARBs, there are also differences. Losartan has significantly less affinity to the type I angiotensin II receptor than valsartan, although the active metabolite of losartan (EXP3174) is a noncompetitive antagonist of the receptor.[107] Regarding hemodialysis patients specifically, Gamboa *et al* compared effects of valsartan and ramipril in a small crossover trial ($n = 15$).[108] The study found that ramipril, but not valsartan, conferred pro-inflammatory effects that might mediate increased cardiovascular risk.

An important aspect of efficacy is dose achievement. In the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial, high-risk heart failure patients were randomized to receive either 32.5-35.0 mg/day or 2.5-5.0 mg/day of lisinopril.[109]

Patients who received the high dose experienced 12% lower risk of death or hospitalization and 24% fewer admissions for heart failure. In the HEALL trial of high-dose (150 mg/day) versus low-dose (50 mg/day) losartan, those who received the high dose experienced 13% fewer admissions for heart failure.[110] We found that roughly 50% to 60% of patients that received valsartan were dispensed the target dose of 320 mg/day. On the other hand, more than half of lisinopril users were dispensed doses of 20 mg/day or less. Although we could not identify the reasons for relatively low doses of lisinopril in the study cohort, of concern is the possibility that patients could not tolerate upward titration.

This study has several limitations. First, unmeasured confounding may exist. We adjusted for baseline differences in demographic and comorbid factors, but cannot exclude the possibility that groups of patients were channeled to some agents. For example, descriptive data suggest that ramipril users were older, more likely to be white, and less likely to be subsidized than users of all other agents. Second, risk contrasts were functions of available formulations of the 6 agents in 2007-2011. Ramipril became available in generic form in 2008, losartan in 2010, and valsartan in 2012 (*i.e.*, after the end of the study era). It is uncertain whether relative risks associated with branded and generic forms of valsartan are equivalent. Third, available sample size constrained the precision of relative risk estimates. In order to improve precision, we included patients with and without exposure to ACE inhibitors or ARBs during the 3-month interval preceding index hospitalization. Future studies should confirm study findings in cohorts comprising new users.

In conclusion, we found heterogeneous hazards of death and hospitalization associated with exposure to 4 ACE inhibitors and 2 ARBs in hemodialysis patients with heart failure. These data suggest that clinical outcomes may be improved by substituting valsartan for lisinopril at the time of discharge from hospitalization principally for heart failure. The reasons for lower risk of death and hospitalization in valsartan users are unclear, but lower risk may reflect the relatively high proportion of valsartan users who were dispensed target doses of 320 mg/day. More studies are needed to clarify the generalizability of results, including whether valsartan is superior to all ACE inhibitors and whether valsartan is associated with lowest risk among ACE inhibitors and ARBs in dialysis patients without heart failure.

Table 5-1. Characteristics of exposed patients, by agent, among HF cases ascertained from the principal diagnosis

	ACE inhibitors				ARBs		ASD [a]
	Benazepril	Enalapril	Lisinopril	Ramipril	Losartan	Valsartan	
Sample size	457	685	3854	304	624	1208	
Age [b] (years)	63.8 (12.5)	64.4 (13.4)	64.4 (13.7)	66.9 (13.3)	65.5 (13.2)	64.8 (13.7)	3.3
Race (%)							
White	48.4	47.7	49.5	55.9	50.0	49.4	0.2
Black	45.5	49.9	47.1	40.5	42.5	42.7	8.8
Asian	6.1	2.3	3.4	3.6	7.5	7.9	19.6
Sex (%)							
Female	53.4	48.6	50.6	51.0	58.7	58.6	16.1
Male	46.6	51.4	49.4	49.0	41.4	41.4	16.1
Primary cause of ESRD (%)							
Diabetes	50.1	45.7	45.6	51.3	47.6	50.6	10.1
Hypertension	36.5	32.0	32.9	28.0	31.4	30.3	5.5
Polycystic kidney disease	6.1	8.3	8.7	7.2	8.5	8.0	2.4
Glomerulonephritis	0.9	2.9	1.7	2.6	1.3	1.2	3.9
Other cause	5.0	7.9	8.2	9.2	8.0	7.5	2.3
Unknown cause	1.3	3.2	3.0	1.6	3.2	2.4	9.8
ESRD duration [b] (years)	4.4 (3.5)	5.1 (4.3)	4.9 (4.1)	4.9 (4.2)	5.1 (4.1)	5.0 (4.3)	2.3
Low-income subsidy reciept [b] (%)							
Not subsidized	14.2	21.0	22.1	29.3	22.4	17.5	11.5
Subsidized, without Medicaid	10.7	10.2	11.2	8.2	9.6	9.1	7.0
Subsidized, with Medicaid	75.1	68.8	66.7	62.5	68.0	73.4	14.7
Risk scores [c]							
Liu score	6.1 (4.0)	6.8 (4.0)	6.6 (4.0)	7.0 (3.9)	6.7 (4.1)	6.5 (3.8)	2.8
van Walraven score	15.6 (9.4)	17.2 (10.0)	16.6 (9.6)	17.6 (10.0)	16.6 (9.6)	16.4 (9.3)	2.1
Medication score 1	-5.9 (7.7)	-7.4 (8.4)	-7.6 (8.4)	-5.5 (8.3)	-8.3 (8.8)	-8.2 (8.5)	7.4
Medication score 2	-5.1 (7.4)	-6.7 (8.4)	-7.1 (9.0)	-5.7 (8.5)	-7.9 (9.2)	-7.3 (8.6)	2.4
Medication score 3	9.0 (8.5)	8.8 (8.8)	8.9 (8.6)	9.7 (8.8)	8.5 (8.4)	8.8 (8.6)	0.5
Medication score 4	13.3 (8.4)	12.8 (7.9)	13.0 (8.4)	13.2 (8.2)	12.9 (8.0)	13.4 (8.1)	4.2
Body mass index [d] (kg / m^2)	27.8 (6.5)	27.0 (6.3)	27.3 (6.7)	27.9 (6.9)	27.8 (6.5)	27.7 (6.7)	6.8

Hematocrit [e] (%)	33.8 (2.9)	33.7 (3.0)	33.6 (3.0)	33.7 (2.9)	33.6 (3.0)	33.7 (2.8)	1.1
Hospitalization history [d] (days)	6.3 (10.3)	8.3 (13.7)	7.3 (12.0)	8.2 (16.5)	6.5 (10.6)	7.1 (11.8)	1.7
Kidney transplant waitlist registration [b] (%)	11.8	14.0	11.5	9.5	14.7	14.5	8.8
ESA exposure [e]							
No exposure (%)	4.4	5.4	3.9	4.0	3.7	2.9	5.6
Darbepoetin alfa dose [f] (mcg)	811 (520)	1056 (815)	770 (769)	763 (654)	888 (946)	895 (744)	16.6
Epoetin alfa dose [f] (1000s IU)	245 (226)	229 (204)	240 (215)	229 (199)	235 (216)	246 (218)	2.8
Intravenous VDA exposure							
No exposure (%)	16.2	17.7	15.7	16.8	17.0	14.9	2.2
Calcitriol dose [f] (mcg)	31 (20)	39 (34)	47 (37)	17 (14)	39 (56)	31 (32)	46.8
Doxercalciferol dose [f] (mcg)	138 (83)	130 (84)	134 (90)	128 (73)	147 (97)	126 (84)	10.0
Paricalcitol dose [f] (mcg)	174 (123)	174 (135)	175 (138)	202 (158)	180 (134)	170 (135)	3.7
RAS inhibitor exposure [e] (%)	79.7	71.1	66.4	65.5	79.3	82.2	36.8
Dialysis provider [b] (%)							
Fresenius Medical Care	36.1	34.0	34.5	34.5	31.3	30.9	7.7
DaVita	30.9	27.0	31.3	21.7	30.9	33.2	4.1
Dialysis Clinic, Inc. (DCI)	4.2	2.0	4.4	4.0	3.9	2.6	9.8
Small dialysis organization	10.9	10.7	10.2	10.5	10.7	10.5	1.0
Independent dialysis provider	15.1	19.6	11.6	16.5	15.9	16.8	15.0
Hospital-based dialysis provider	2.8	6.7	8.1	12.8	7.4	6.0	8.0
Co-incident myocardial infarction [g] (%)	2.8	2.3	2.9	2.6	4.0	2.6	2.2
Specialty care during HF hospitalization (%)							
Cardiologist	72.4	80.6	80.1	79.9	79.0	77.4	6.6
Nephrologist	82.7	82.0	86.4	85.5	85.6	84.8	4.5
Pulmonologist	17.3	18.1	16.3	16.5	20.5	19.4	8.0
Procedures during HF hospitalization (%)							
Coronary catheterization	10.3	13.3	10.5	13.2	10.7	11.5	3.1
Echocardiogram	27.1	29.3	25.7	31.3	27.9	25.6	0.2
Electrocardiogram	71.3	76.6	76.8	76.6	78.2	76.2	1.2
Exercise electrocardiography	9.0	8.0	9.0	7.9	7.1	8.8	0.9
Myocardial perfusion scintigraphy	7.2	6.9	6.6	7.6	6.3	5.8	3.2
Length of stay [g] (days)	4.0 (3.0)	4.5 (3.5)	4.1 (3.5)	4.3 (3.9)	4.2 (3.8)	4.2 (3.2)	1.2
Discharge location (%)							
Home, under self-care	85.8	82.9	82.2	79.3	79.8	82.9	1.9

Home health agency	14.2	17.1	17.9	20.7	20.2	17.1	1.9
Early rehospitalization [h] (%)	9.9	9.8	11.1	11.5	9.5	10.8	1.1
Concomitant exposure [h] (%)							
Beta blocker	49.0	53.3	53.9	54.3	48.9	50.6	6.6
Digoxin	0.7	4.1	2.5	4.3	2.4	2.0	3.4

Note: For quantities not displayed as percentages, summaries are displayed as mean and standard deviation (in parentheses).

Abbreviations: ASD, absolute standardized difference; HF, heart failure; ESA, erythropoiesis-stimulating agent; ESRD, end stage renal disease; IU, international units; VDA, vitamin D analogue.

[a] Difference between valsartan users and lisinopril users, in percentage of 1 standard deviation.

[b] At the start of risk.

[c] During the 12 months before admission for heart failure.

[d] During the 6 months before admission for heart failure.

[e] During the 3 months before admission for heart failure.

[f] Among patients with at least one administration.

[g] During hospitalization for heart failure.

[h] Between discharge and the start of risk.

Table 5-2. Daily dose distributions during the first 12 months of on-treatment follow-up

	Time since date of first fill				
	0 Months	3 Months	6 Months	9 Months	12 Months
Sample size	7132	3769	2100	1347	919
ACE inhibitors					
Benazepril (%)					
5 mg	5.5	3.3	2.1	2.4	1.2
10 mg	14.0	11.8	12.3	12.0	9.6
20 mg	33.0	30.2	32.6	34.4	36.1
40 mg	39.8	44.9	44.9	44.8	47.0
80 mg	7.7	9.8	8.0	6.4	6.0
Enalapril (%)					
2.5 mg	10.4	8.4	7.5	7.6	7.7
5 mg	15.0	12.8	9.1	5.3	4.3
10 mg	20.1	18.1	17.4	16.5	13.7
20 mg	27.0	27.0	27.0	28.2	30.8
40 mg	27.4	33.7	39.0	42.4	43.6
Lisinopril (%)					
2.5 mg	9.2	6.9	5.7	5.3	4.2
5 mg	12.9	10.5	9.3	8.6	8.1
10 mg	19.0	16.4	15.1	14.4	12.9
20 mg	20.9	22.4	21.6	21.9	23.2
40 mg	30.4	34.0	38.2	37.8	39.2
80 mg	7.5	9.9	10.1	12.0	12.3
Ramipril (%)					
2.5 mg	25.7	22.5	19.2	17.6	20.0
5 mg	22.7	20.9	22.1	30.9	26.7
10 mg	36.8	36.8	39.4	35.3	42.2
20 mg	13.2	17.0	18.3	14.7	8.9
40 mg	1.6	2.7	1.0	1.5	2.2

ARBs					
Losartan (%)					
25 mg	12.3	10.1	7.0	5.6	5.6
50 mg	28.2	24.2	22.9	21.3	18.3
100 mg	57.7	63.5	67.4	69.1	72.2
200 mg	1.8	2.2	2.7	3.9	4.0
Valsartan (%)					
40 mg	1.6	4.4	3.7	4.7	4.7
80 mg	17.1	15.0	12.7	12.4	12.0
160 mg	28.6	27.9	24.7	25.0	24.5
320 mg	49.8	52.7	58.9	58.0	58.8

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.

Table 5-3. Event counts and crude event rates, by agent

	ACE inhibitors				ARBs	
	Benazepril	Enalapril	Lisinopril	Ramipril	Losartan	Valsartan
Patient-years at risk						
Intention-to-treat	764	1151	5858	458	983	2018
On-treatment	277	393	2308	173	414	814
All-cause mortality						
Intention-to-treat	201	302	1688	162	261	483
	(26)	(26)	(29)	(35)	(27)	(24)
On-treatment	60	85	559	54	72	149
	(22)	(22)	(24)	(31)	(17)	(18)
All-cause hospitalization						
Intention-to-treat	2217	3410	17,844	1286	2924	5712
	(305)	(313)	(321)	(295)	(313)	(297)
On-treatment	757	1118	6775	479	1189	2197
	(285)	(297)	(305)	(288)	(299)	(280)

Note: For events, summaries are displayed as cumulative count and rate per 100 patient-years (in parentheses).

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.

Table 5-4. Adjusted hazard ratios of death for pairwise comparisons of ACE inhibitors and ARBs, by follow-up rule

	ACE inhibitors				ARBs	
	Benazepril	Enalapril	Lisinopril	Ramipril	Losartan	Valsartan
Intention-to-treat						
ACE inhibitors						
Benazepril		1.09 (0.90-1.31)	0.96 (0.82-1.13)	0.84 (0.67-1.05)	1.00 (0.82-1.20)	1.15 (0.96-1.37)
Enalapril	0.92 (0.76-1.12)		0.89 (0.77-1.01)	**0.77 (0.62-0.95)**	0.92 (0.77-1.08)	1.06 (0.91-1.22)
Lisinopril	1.04 (0.88-1.22)	1.13 (0.99-1.30)		0.87 (0.73-1.04)	1.04 (0.92-1.18)	**1.19 (1.07-1.33)**
Ramipril	1.20 (0.95-1.50)	**1.30 (1.06-1.60)**	1.15 (0.96-1.36)		1.19 (0.96-1.45)	**1.37 (1.13-1.66)**
ARBs						
Losartan	1.00 (0.83-1.22)	1.09 (0.92-1.29)	0.97 (0.85-1.09)	0.84 (0.69-1.04)		1.15 (0.99-1.34)
Valsartan	0.87 (0.73-1.04)	0.95 (0.82-1.10)	**0.84 (0.75-0.94)**	**0.73 (0.60-0.89)**	0.87 (0.75-1.01)	
On-treatment						
ACE inhibitors						
Benazepril		0.98 (0.67-1.43)	0.90 (0.67-1.21)	0.76 (0.52-1.11)	1.19 (0.82-1.72)	1.16 (0.83-1.59)
Enalapril	1.02 (0.70-1.49)		0.92 (0.71-1.17)	0.78 (0.54-1.13)	1.21 (0.85-1.70)	1.18 (0.88-1.57)
Lisinopril	1.11 (0.83-1.49)	1.08 (0.85-1.41)		0.84 (0.63-1.15)	**1.31 (1.02-1.71)**	**1.28 (1.05-1.57)**
Ramipril	1.32 (0.90-1.94)	1.29 (0.89-1.96)	1.19 (0.87-1.58)		**1.56 (1.07-2.25)**	**1.52 (1.09-2.14)**
ARBs						
Losartan	0.84 (0.58-1.22)	0.83 (0.59-1.17)	**0.76 (0.59-0.98)**	**0.64 (0.44-0.93)**		0.97 (0.72-1.29)

Valsartan	0.87 (0.63-1.20)	0.85 (0.64-1.13)	**0.78 (0.64-0.96)**	**0.66 (0.47-0.91)**	1.03 (0.77-1.39)

Note: Hazard ratios are interpreted as hazard associated with agent in row, relative to agent in column; for example, the intention-to-treat hazard ratio of death for valsartan versus benazepril was 0.87. Statistically significant contrasts ($P < 0.05$) are displayed in boldface type.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.

Table 5-5. Adjusted hazard ratios of hospitalization for pairwise comparisons of ACE inhibitors and ARBs, by follow-up rule

	ACE inhibitors				ARBs	
	Benazepril	Enalapril	Lisinopril	Ramipril	Losartan	Valsartan
Intention-to-treat						
ACE inhibitors						
Benazepril		1.06 (0.93-1.19)	1.02 (0.92-1.14)	1.08 (0.93-1.26)	1.00 (0.88-1.12)	1.10 (0.98-1.24)
Enalapril	0.95 (0.84-1.08)		0.97 (0.89-1.04)	1.02 (0.90-1.18)	0.94 (0.86-1.04)	1.05 (0.95-1.15)
Lisinopril	0.98 (0.88-1.08)	1.03 (0.96-1.12)		1.06 (0.94-1.19)	0.98 (0.91-1.05)	**1.08 (1.01-1.16)**
Ramipril	0.92 (0.79-1.08)	0.98 (0.85-1.11)	0.94 (0.84-1.06)		0.92 (0.80-1.05)	1.02 (0.90-1.06)
ARBs						
Losartan	1.00 (0.89-1.13)	1.06 (0.96-1.17)	1.03 (0.95-1.10)	1.09 (0.95-1.24)		**1.11 (1.02-1.21)**
Valsartan	0.91 (0.81-1.02)	0.96 (0.87-1.06)	**0.93 (0.87-0.99)**	0.98 (0.86-1.11)	**0.90 (0.83-0.98)**	
On-treatment						
ACE inhibitors						
Benazepril		1.04 (0.88-1.20)	0.98 (0.86-1.11)	1.05 (0.87-1.25)	0.95 (0.81-1.11)	1.06 (0.90-1.24)
Enalapril	0.97 (0.83-1.14)		0.95 (0.85-1.05)	1.01 (0.86-1.19)	0.92 (0.80-1.15)	1.03 (0.89-1.17)
Lisinopril	1.02 (0.90-1.16)	1.06 (0.95-1.17)		1.07 (0.93-1.22)	0.97 (0.88-1.07)	1.09 (0.97-1.20)
Ramipril	0.96 (0.80-1.16)	0.99 (0.84-1.16)	0.94 (0.82-1.07)		0.91 (0.78-1.07)	1.02 (0.85-1.19)
ARBs						
Losartan	1.05 (0.90-1.23)	1.09 (0.95-1.25)	1.03 (0.93-1.14)	1.10 (0.93-1.28)		1.12 (0.98-1.26)

Valsartan	0.94 (0.80-1.11)	0.97 (0.85-1.12)	0.92 (0.84-1.03)	0.98 (0.84-1.17)	0.89 (0.79-1.02)

Note: Hazard ratios are interpreted as hazard associated with agent in row, relative to agent in column; for example, the intention-to-treat hazard ratio of death for valsartan versus benazepril was 0.91. Statistically significant contrasts ($P < 0.05$) are displayed in boldface type.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.

Table 5-6. Proportions of days covered with supplied medication, by on-treatment follow-up rule

	Maximum gap between supplies		
	1 month	2 months	3 months
ACE inhibitors			
Benazepril	75.7 (74.2-77.3)	69.4 (67.5-71.4)	66.6 (64.5-68.8)
Enalapril	72.9 (71.6-74.2)	66.0 (64.4-67.6)	62.6 (60.8-64.3)
Lisinopril	74.2 (73.6-74.8)	68.4 (67.7-69.1)	65.7 (64.9-66.5)
Ramipril	73.1 (71.2-74.9)	66.4 (63.9-68.8)	62.5 (59.7-65.2)
ARBs			
Losartan	75.4 (74.1-76.7)	69.6 (67.8-71.2)	66.6 (64.7-68.5)
Valsartan	75.6 (74.6-76.6)	70.0 (68.8-71.3)	67.1 (65.7-68.5)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.

Figure 5-1A. Unadjusted survival by initial RAS inhibitor agent in intention-to-treat follow-up

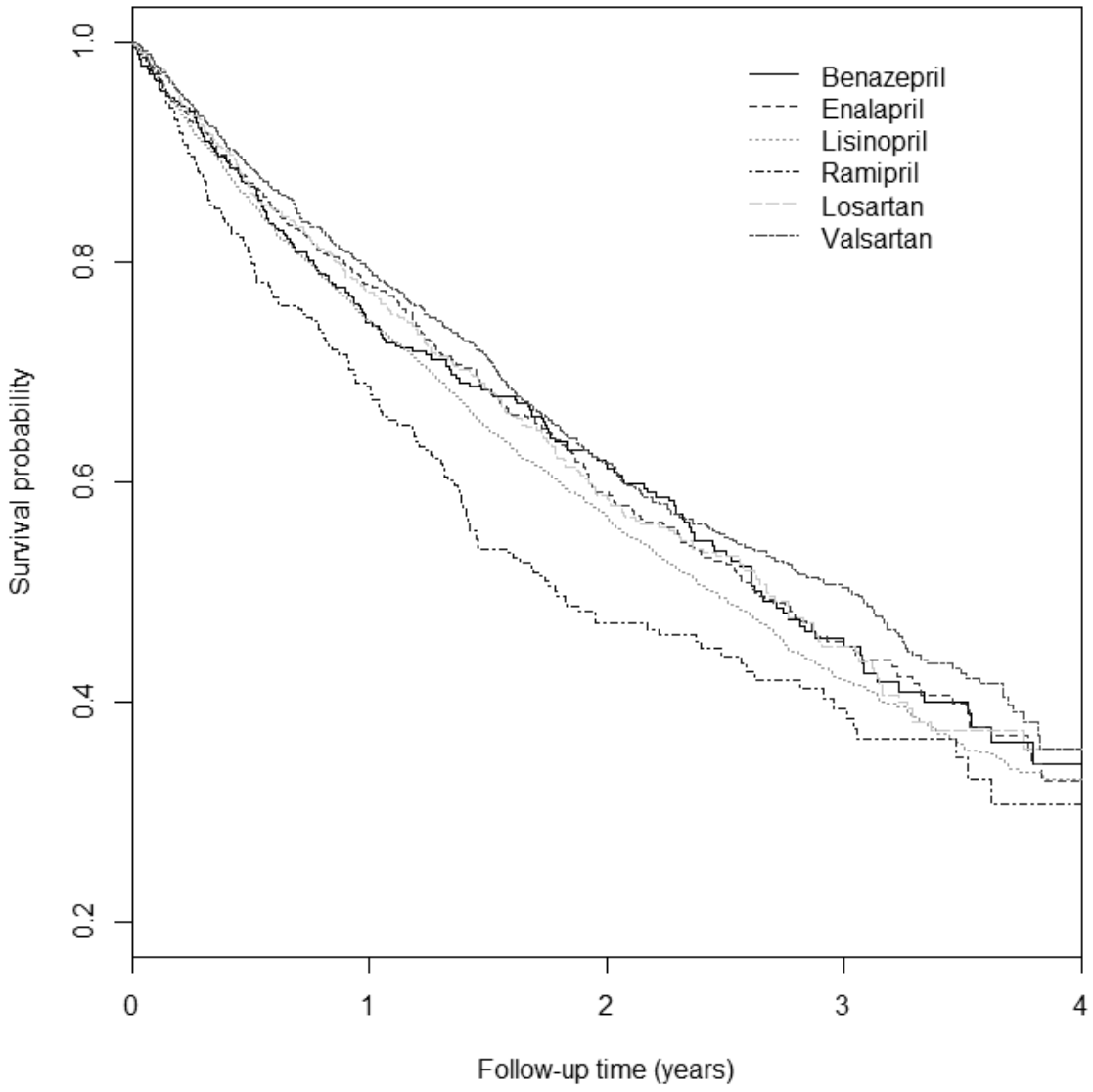


Figure 5-1B. Unadjusted survival by initial RAS inhibitor agent in on-treatment follow-up

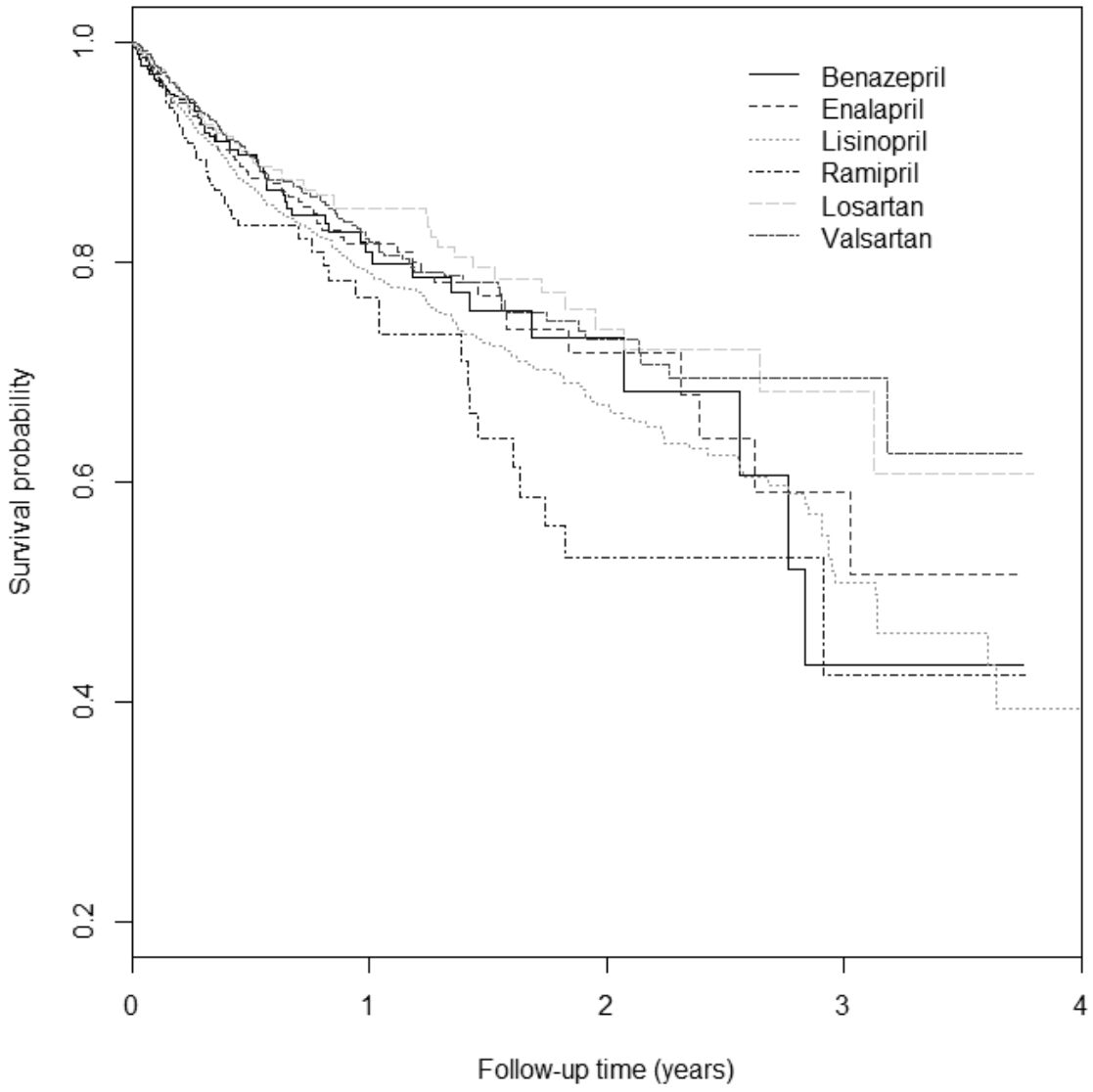


Figure 5-2A. Bootstrapped probabilities of ranks of relative hazards associated with initial RAS inhibitor agents, for death in intention-to-treat follow-up

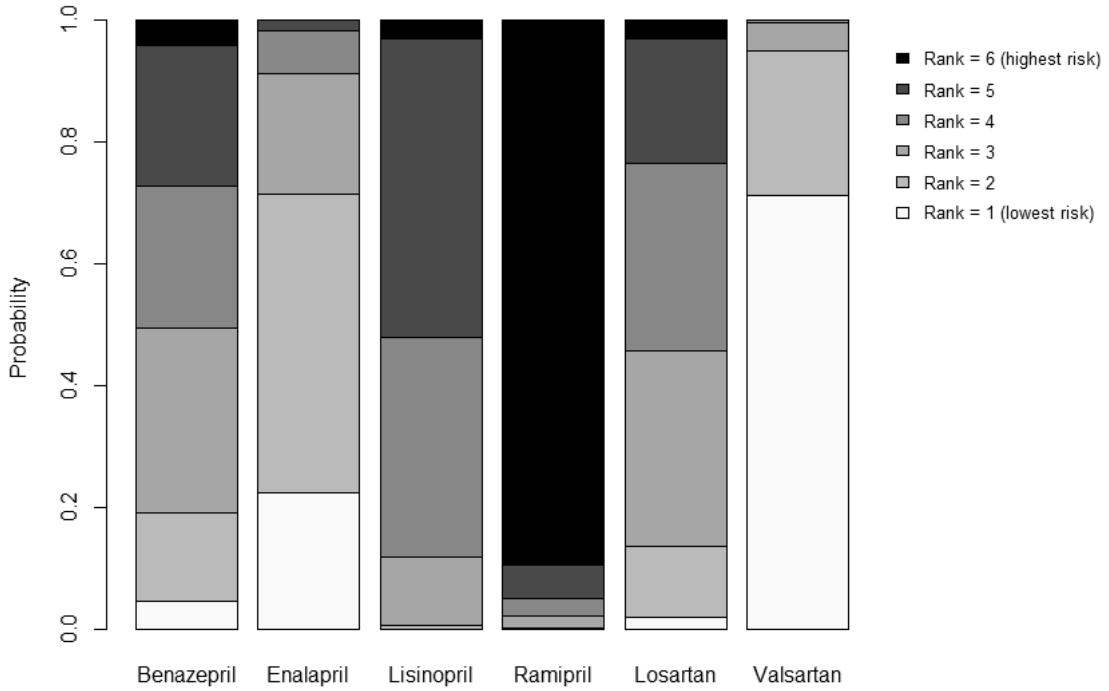


Figure 5-2B. Bootstrapped probabilities of ranks of relative hazards associated with initial RAS inhibitor agents, for death in on-treatment follow-up

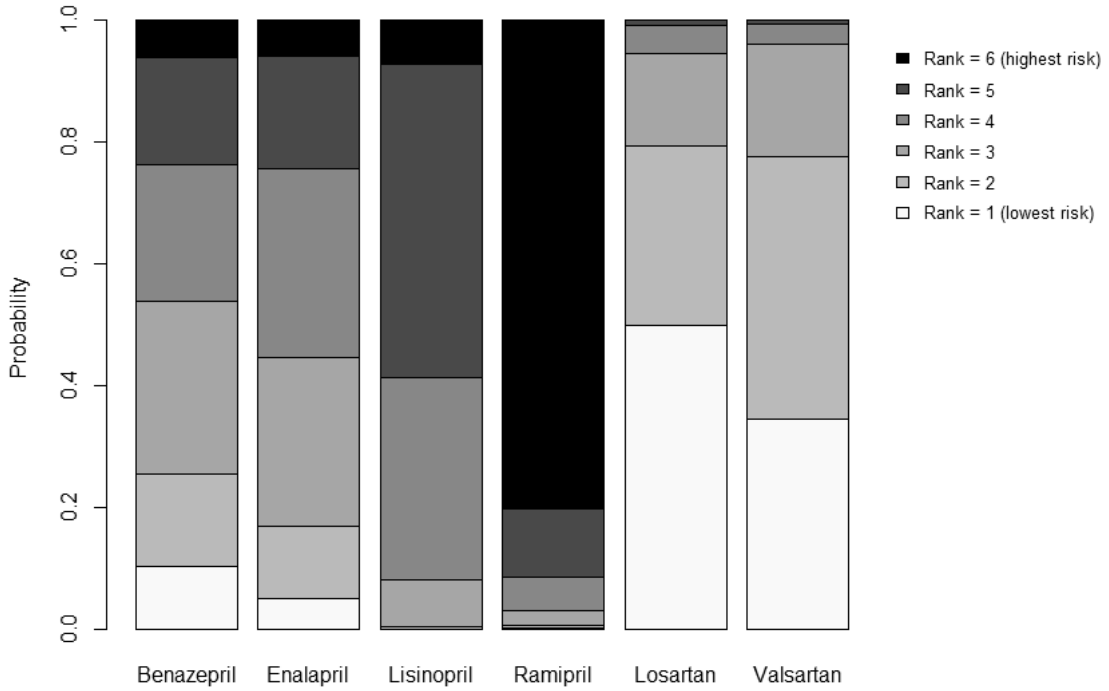


Figure 5-2C. Bootstrapped probabilities of ranks of relative hazards associated with initial RAS inhibitor agents, for hospitalization in intention-to-treat follow-up

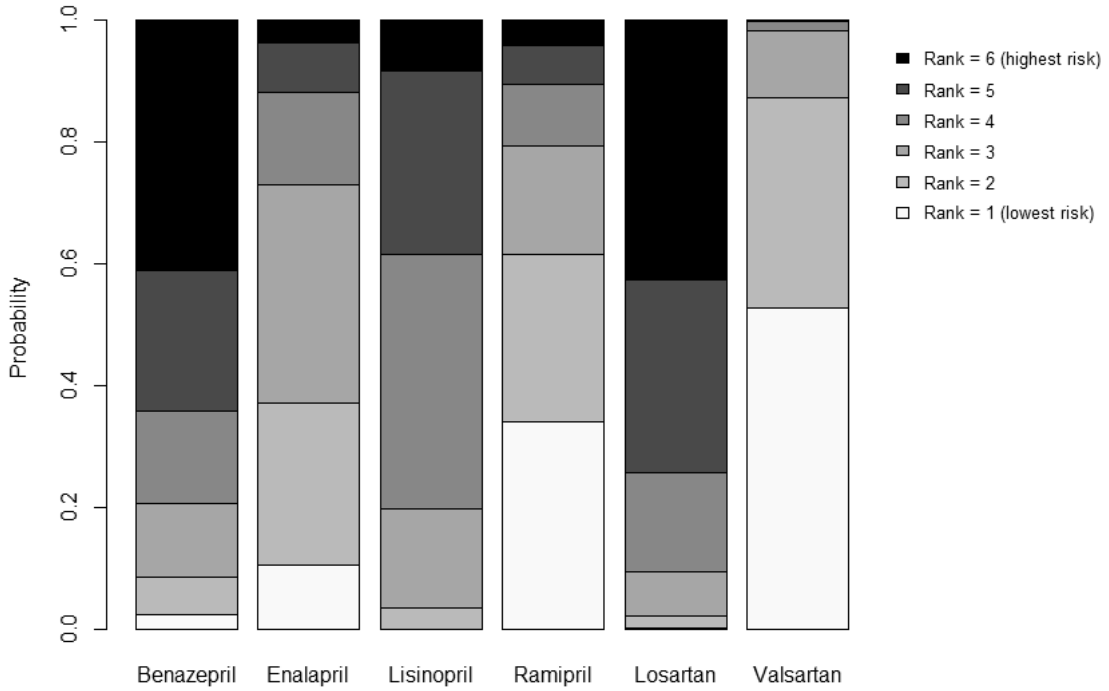


Figure 5-2D. Bootstrapped probabilities of ranks of relative hazards associated with initial RAS inhibitor agents, for hospitalization in on-treatment follow-up

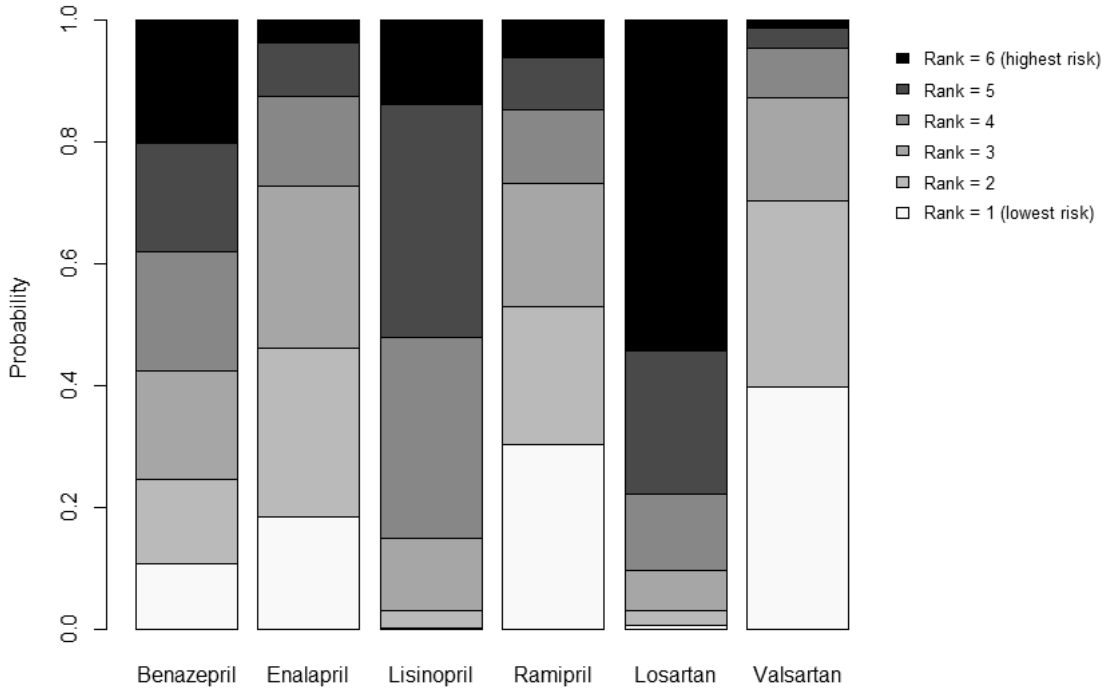


Figure 5-3. Cumulative incidence of RAS inhibitor interruption, by initial RAS inhibitor agent.

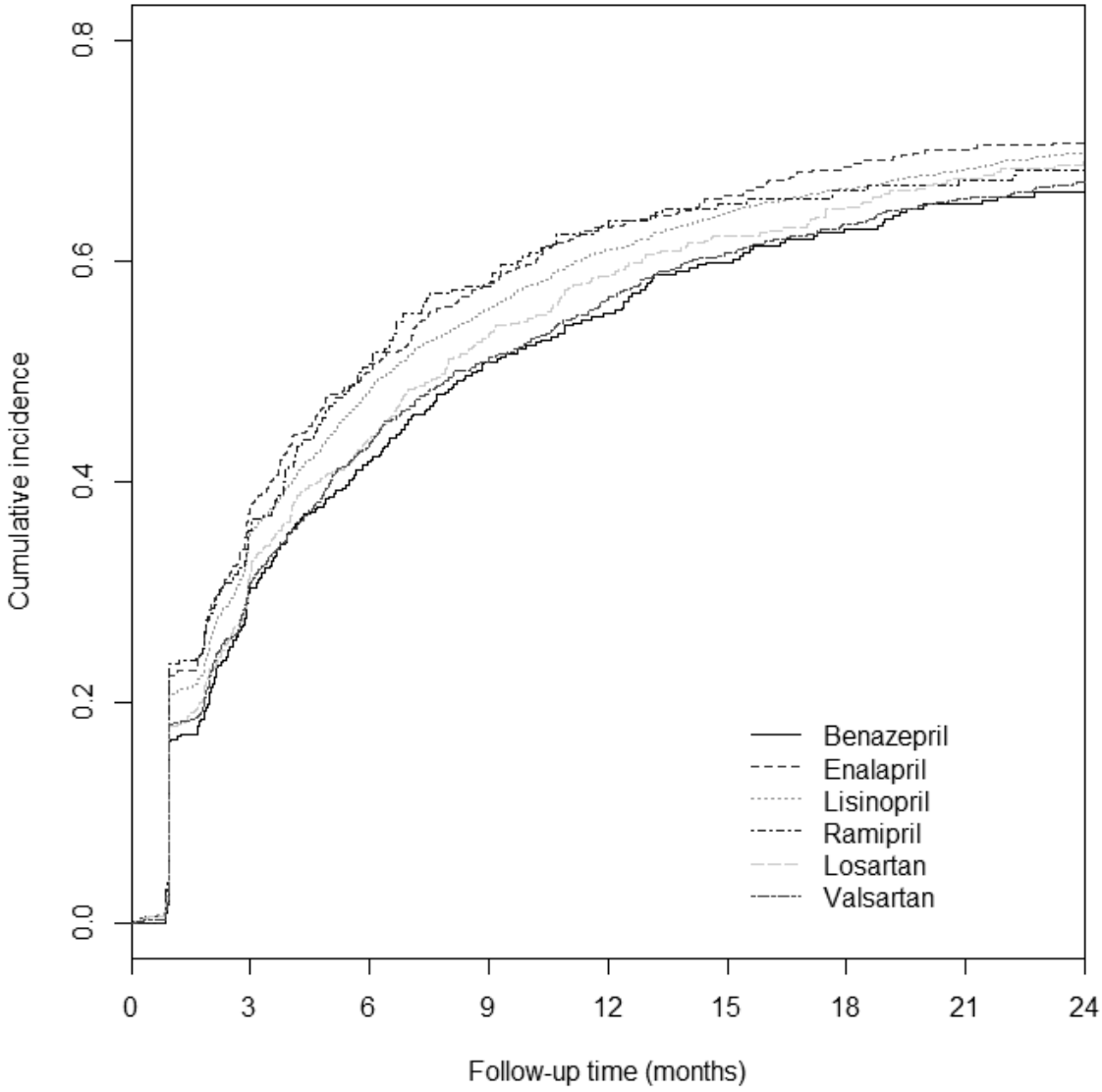
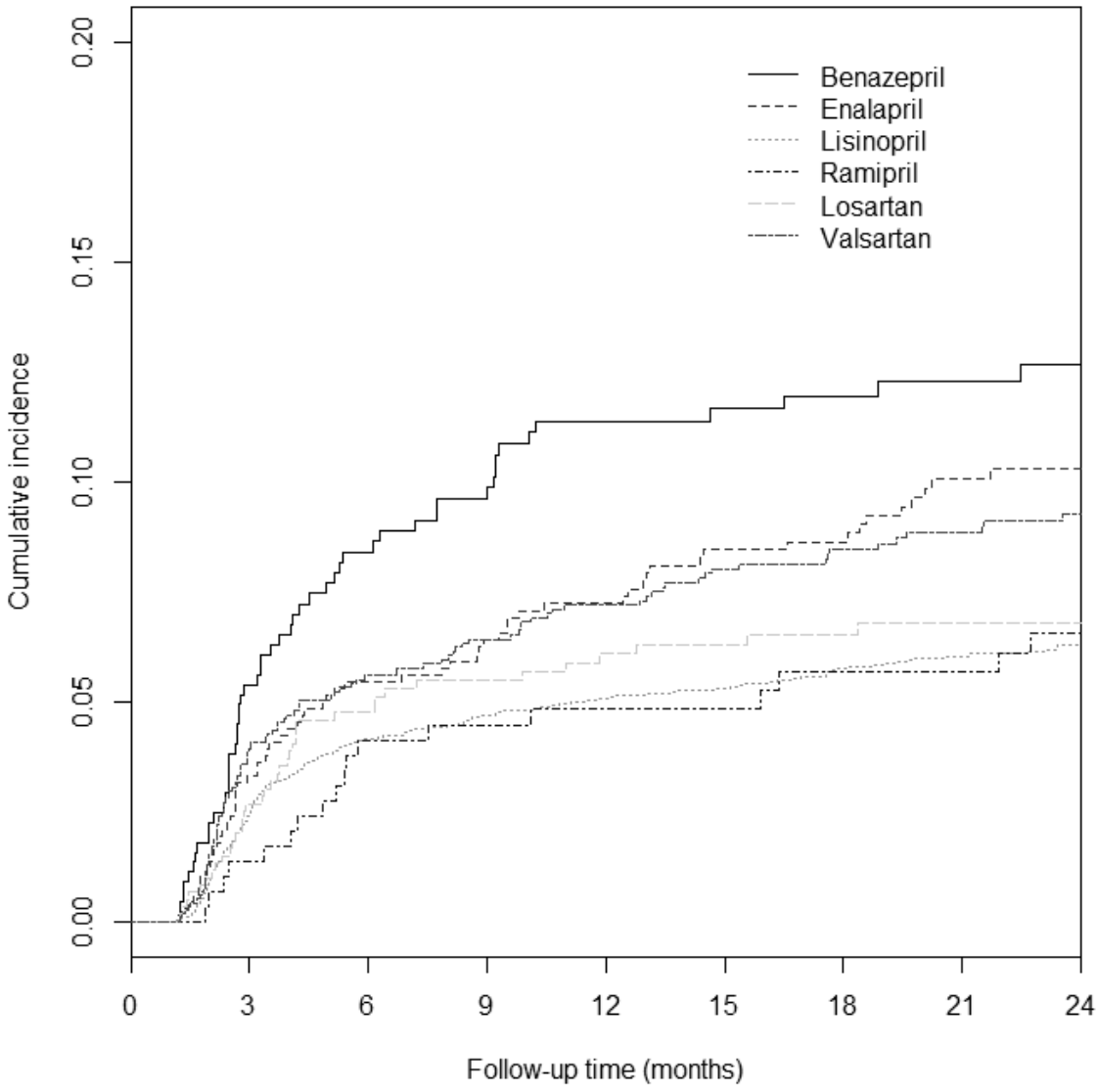


Figure 5-4. Cumulative incidence of treatment group crossover (to another RAS inhibitor), by initial RAS inhibitor agent.



Chapter 6

Conclusion

The studies in this dissertation collectively demonstrate the potential of Medicare Part D claims to improve epidemiologic methodology, as well as to create clinical evidence in disease states characterized by a paucity of high-quality studies (*i.e.*, randomized clinical trials). In the first study, I constructed risk scores based on prescription drug claims in dialysis patients. In the second study, I assessed the efficacy and safety of ACE inhibitors and ARBs in heart failure on dialysis. In the third study, I assessed the relative hazards of death and hospitalization for 4 ACE inhibitors and 2 ARBs and applied nonparametric bootstrapping to neatly summarize rankings of the 6 agents. Although each study has important limitations, each study also opens new avenues for further exploration, both in dialysis patients and in patients without ESRD.

Risk scores can be useful tools in clinical and epidemiologic settings. The ubiquity of the Charlson Comorbidity Index in epidemiologic studies across diverse disease states is proof of concept. However, risk scores should in principle be designed to reflect important comorbid conditions, biochemical concentrations, or medication exposures in the disease state of interest. I constructed multiple risk scores that can be used in dialysis patients. Of course, it is cumbersome to use unique scores for different outcomes at different points in the natural history of a disease. In light of the results of the first study of this dissertation, the outstanding challenge is to create a unifying risk score that can be used in studies of mortality and morbidity alike, possibly with scaling factors for point values to reflect the modifying influence of time since dialysis initiation. More generally, the algorithm that I have proposed can be applied to patients without

ESRD. For example, scores based on prescription drug claims might be developed for patients with CKD Stage 3 or Stage 4 or for patients with other pathologies, such as cardiovascular disease. In the grandest scheme, risk scores could be constructed (and updated) for dozens of disease states and then mapped to a common scale, such that the calculation and interpretation of scores could be automated by electronic health record systems and results could be packaged for patients.

The efficacy of ACE inhibitors and ARBs for the treatment of heart failure with reduced ejection fraction is well-established in patients with normal renal function. Very little data, however, exist to support their use in patients with kidney failure. Because all ACE inhibitors and an increasing number of ARBs are available in generic formulations, there is very little likelihood of a large randomized clinical trial of a RAS inhibitor versus placebo in dialysis patients with heart failure. In the absence of trial evidence, physicians must rely on observational studies to inform clinical practice. I used Medicare Parts A, B, and D claims to identify patients who were discharged from hospitalization principally for heart failure and then dispensed an ACE inhibitor or ARB. I also applied propensity score matching to identify controls that were similar (on average) to exposed patients with respect to dozens of patient characteristics. The study suggested that treatment with an ACE inhibitor or ARB was associated with significant reductions in the risk of death and hospitalization after discharge.

For frame of reference, the present study included more than 18 times the number of patients that were enrolled in the FOSIDIAL trial of fosinopril versus placebo in hemodialysis patients with left ventricular hypertrophy. Of course, observational studies can never eliminate the possibility of unmeasured confounding. However, the inherent

flexibility of the retrospective cohort study design admits easy application of alternative case definitions, exposure definitions, outcomes, and follow-up rules. Therefore, the robustness of findings can be assessed, even if the absence of unmeasured confounding cannot be assured. Ultimately, the present study raises a number of important questions. First, it is unknown whether initiation of treatment with an ACE inhibitor or ARB after first diagnosis of heart failure in the outpatient setting is more or less efficacious than treatment after first hospitalization principally for heart failure. Second, it is unknown whether the results of the study apply similarly to heart failure with reduced EF and heart failure with preserved EF. Third, it remains uncertain whether ACE inhibitors and ARBs are associated with similar reductions in risk, primarily because of the limited number of ARB users in the present study. Fourth, the influence of the concurrent use of beta blockers is unclear. The identification of matching treatment groups defined by use of RAS inhibitors, beta blockers, or both is needed in future research.

Within subclasses of ACE inhibitors and ARBs, the selection of a specific agent may be capricious or merely dictated by formulary design. Resources are likely unavailable to compare agents in large randomized clinical trials. However, in an era with large administrative databases and in the context of Medicare Part D, which has a core benefit structure but includes dozens of unique formularies, there are growing opportunities to compare outcomes across multiple agents in a single subclass. I compared the risks of death and hospitalization associated with exposure to benazepril, enalapril, lisinopril, ramipril, losartan, and valsartan in dialysis patients that had been discharged from hospitalization principally for heart failure. The study suggested that the choice of an RAS inhibitor agent may be consequential. In particular, valsartan, which

became available in generic form very recently, was associated with relatively low risk of mortality and morbidity, thereby questioning the dominance of lisinopril in dialysis patients. Interestingly, daily doses of supplied valsartan were more likely than any other agent to be maximized. The preeminent challenge with this line of inquiry is sample size and the associated precision of relative risk estimates. More cases, primarily from additional years of data, are needed to confirm findings. Of course, the ongoing evolution of marketed medications presents a challenge of its own. For example, it cannot be assumed that generic forms of valsartan are as effective as the branded form ("Diovan"), particularly in light of problems with major generic drug manufacturers. The continued investigation of heterogeneity in outcomes associated with agents that have similar or identical mechanisms of action is likely needed to achieve incremental gains in quality of care.

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Appendix 1

Revisions to harmonize definitions across combinations of cohort and event and to improve relevance in dialysis patients comprised the following:

a. The subclass of miscellaneous anti-infective agents (GPI, 160000) was limited to agents indicated for *Clostridium difficile* colitis, because metronidazole was the most frequently dispensed item in the subclass. In addition, the associations of the subclass with risks of mortality and hospitalization were closely approximated by corresponding associations with metronidazole and (oral) vancomycin.

b. The subclass of progestins indicated for cancer (GPI, 214040) was limited to megestrol acetate, because megestrol was the only item dispensed to patients and was more likely prescribed to treat anorexia or cachexia than to treat cancer.

c. The subclass of vasopressors (GPI, 380000) was limited to midodrine hydrochloride, because midodrine was the only item dispensed to patients.

d. The subclass of adrenergic bronchodilator combination agents (GPI, 442099) was limited to ipratropium/albuterol, because that combination was the most frequently dispensed item in the subclass. In addition, ipratropium/albuterol was pooled with the subclass of anticholinergic bronchodilators (GPI, 441000).

e. The subclass of bowel evacuant combination agents (GPI, 469920) was limited to agents containing polyethylene glycol 3350, because those combinations were the only items dispensed to patients.

f. The subclass of gastrointestinal stimulants (GPI, 523000) was limited to metoclopramide hydrochloride, because metoclopramide was the only item dispensed to patients.

g. The subclass of miscellaneous anticonvulsants (GPI, 726000) was limited to gamma-aminobutyric acid analogues, because the associations of the subclass with risks of mortality and hospitalization were closely approximated by corresponding associations with gabapentin and pregabalin.

h. The subclass of topical anesthetic combination agents (GPI, 908599) was limited to lidocaine/prilocaine, because that combination was the only item dispensed to patients was likely prescribed for use during vascular access cannulation.

Appendix 2

The 4 ACE inhibitors and 2 ARBs in this study are briefly described in the following:

Benazepril

Benazepril hydrochloride was approved by the FDA on June 25, 1991. Benazepril is currently available in either branded ("Lotensin") or generic form. The drug is also available in combination with a calcium channel blocker, amlodipine, in either branded ("Lotrel") or generic form; or a diuretic, hydrochlorothiazide, in either branded or generic ("Lotensin HCT") form. Benazepril is indicated only in treatment of hypertension.[111] Randomized clinical trial data about monotherapy with benazepril in heart failure are very limited.

Benazepril is available in potencies of 5, 10, 20, and 40 mg. Benazepril is metabolized to benazeprilat, which has a half-life of roughly 10 to 11 hours. At 24 hours after administration, between 80% and 90% of plasma ACE activity is inhibited. Benazepril is typically administered once per day, although twice-daily regimens may be necessary in patients with inadequate trough responses even after upward titration. Common daily doses range from 20 to 40 mg; cumulative daily doses greater than 80 mg have not been evaluated. Benazeprilat is predominantly excreted by the kidneys; biliary excretion accounts for only 11% to 12% of total clearance. Therefore, in patients with renal impairment, required dosage may be lower. Hemodialysis has little effect on clearance of benazepril and its active metabolite, benazeprilat.

Enalapril

Enalapril maleate was approved by the FDA on December 24, 1985. Enalapril is now available in either branded ("Vasotec") or generic form. Enalapril is available in combination with a diuretic, hydrochlorothiazide, in either branded ("Vaseretic") or generic form. Enalapril has three indications: (1) treatment of hypertension; (2) treatment of HF, typically in combination with a diuretic and digitalis; and (3) to reduce the incidence of overt heart failure and subsequent hospitalization for HF in patients with an ejection fraction $\leq 35\%$.[112]

An important early study of enalapril was the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). In that study, 253 patients with severe heart failure (New York Heart Association functional class IV) were randomized to receive placebo or enalapril. Risk of death was 27% lower in patients treated with enalapril.[112] The efficacy of enalapril was clearly established in the landmark Study of Left Ventricular Dysfunction (SOLVD) Treatment trial.[113] In that study, 2569 patients were randomized to receive placebo or enalapril and followed for up to 55 months. Study participants had symptomatic heart failure with ejection fraction $\leq 35\%$; patients with serum creatinine > 2.5 mg/dL were excluded. Compared to placebo, enalapril was associated with 11% lower risk of death due to any cause and 30% lower risk of hospitalization for heart failure. In the SOLVD Prevention trial, 4228 patients with asymptomatic heart failure (ejection fraction $\leq 35\%$) were assigned to receive placebo or enalapril.[114] Compared to placebo, enalapril was associated with 8% lower risk of death due to any cause and 32% lower risk of hospitalization for heart failure; only the latter contrast was statistically significant.

Enalapril is available in potencies of 2.5, 5, 10, and 20 mg. Enalapril is a prodrug that is hydrolyzed to enalaprilat; in fact, all ACE inhibitors except captopril and lisinopril are prodrugs. The half-life of enalaprilat is approximately 11 hours. Thus, enalapril is often administered two times per day, although once-daily regimens may be sufficient for treatment of hypertension. The presence of food does not significantly alter the absorption of enalapril. Usual daily doses range from 10 to 40 mg. Enalapril and its active metabolite, enalaprilat, are excreted primarily by the kidneys. Because of renal excretion, the required dosage of enalapril is usually lower in patients with impaired renal function. Enalaprilat is removed by dialysis, albeit less rapidly than captopril is removed.

Lisinopril

Lisinopril was approved by the FDA on December 29, 1987. Lisinopril is available in either branded ("Prinivil," "Zestril) or generic form. The drug is also available in combination with a diuretic, hydrochlorothiazide, in either branded ("Prinzide," "Zestoretic") or generic form. Lisinopril has three indications: (1) treatment of hypertension; (2) adjunctive treatment of HF in patients who have failed to respond adequately to a diuretic and digitalis; and (3) to reduce the incidence of death in patients who are hemodynamically stable in the first 24 hours after acute myocardial infarction.[116] Lisinopril is the most frequently prescribed ACE inhibitor in the US. Early trials of lisinopril were short in duration and assessed occurrence of improvement in symptoms of heart failure. Arguably the most important trial of lisinopril in the treatment of heart failure was the Assessment of Treatment with Lisinopril and Survival (ATLAS) study.[117] In that study, 3164 patients were randomized to receive lisinopril at daily doses of either 2.5 to 5.0 mg or 32.5 to 35.0 mg. Study participants had symptomatic heart failure with

ejection fraction ≤ 30%, but just as in SOLVD, participants with serum creatinine > 2.5 mg/dL were excluded. More than 90% of study participants in each arm were successfully titrated to target dose ranges. The hazard ratios of death due to any cause, due to cardiovascular causes, and the composite endpoint of death and hospitalization for heart failure were 0.92, 0.90, and 0.85, respectively, for high versus low doses of lisinopril; only the final contrast, which was not pre-specified, was significant ($P < 0.05$).

Lisinopril is available in potencies of 2.5, 5, 10, 20, 30, and 40 mg. Like captopril, the molecule is not further metabolized. Its half-life is approximately 12 hours. Lisinopril is almost always administered once per day. The presence of food in the gastrointestinal tract does not significantly alter the absorption of lisinopril, but wide inter-subject variability in absorption has been observed. The bioavailability of lisinopril is modestly lower in patients with heart failure. Typical daily doses for treatment of heart failure range from 5 to 20 mg, although less is required in patients with severely impaired renal function (including patients treated with hemodialysis), because lisinopril is excreted exclusively by the kidneys. Lisinopril is removed by dialysis.

Ramipril

Ramipril was approved by the FDA on January 28, 1991. Ramipril is available in either branded ("Altace") or generic form. It is not available in combination with another molecular entity. Ramipril has three indications: (1) treatment of hypertension; (2) to reduce the incidence of myocardial infarction, stroke, or death from cardiovascular causes in patients aged ≥55 years and at high risk of cardiovascular morbidity because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes and the presence of another risk factor (e.g., hypercholesterolemia, hypertension, micro-

albuminuria, or smoking); and (3) to reduce the incidence of overt heart failure, subsequent hospitalization for HF, and death in patients who exhibit clinical symptoms of HF in the first days after acute myocardial infarction.[118] Efficacy of ramipril in treatment of heart failure was established in the Acute Infarction Ramipril Efficacy (AIRE) study.[119] In that study, 2006 patients were randomized to receive placebo or ramipril. Study participants were randomized between 2 and 9 after acute myocardial infarction, if they exhibited clinical signs of heart failure. Compare to placebo, ramipril was associated with a 27% reduction in risk of death and a 26% reduction in risk of hospitalization for heart failure. There was modest evidence that older patients (*i.e.*, age > 65 years) benefited relatively more from treatment with ramipril than younger patients did.

Ramipril is available in potencies of 1.25, 2.5, 5, and 10 mg. Ramipril is almost entirely metabolized in the liver to ramiprilat, which exhibits about 6 times as much inhibitory activity of ACE as ramipril itself. Elimination of ramiprilat is triphasic: an initial decline with a half-life of 4 hours, during which the drug distributes into peripheral compartments; an apparent elimination phase with a half-life of 9 to 18 hours; and a terminal elimination phase with a half-life greater than 50 hours. Ramipril is typically administered twice per day in patients with hypertension or who exhibit symptoms of HF after acute myocardial infarction, but only once per day in older patients at high risk of cardiovascular morbidity; multiple doses per day appear to inhibit ACE activity more completely in the 24 hours following administration than do single doses. Presence of food in the gastrointestinal tract does not significantly alter the absorption of ramipril. Usual cumulative daily doses vary by indication. In patients with hypertension, doses range from 2.5 to 20 mg per day. In older patients at high risk of cardiovascular

morbidity and in those who exhibit symptoms of HF after acute myocardial infarction, doses of 10 mg per day are often prescribed. In patients with either hepatic or renal impairment, the required dosage may be lower. Whether dialysis removes ramipril or its active metabolite, ramiprilat, remains unknown.

Losartan

Losartan potassium was approved by the FDA on April 14, 1995. It is the oldest ARB that is available for human prescription in the US. Losartan is currently available in either branded ("Cozaar") or generic form. The drug is also available in combination with a diuretic, hydrochlorothiazide, in either branded ("Hyzaar") or generic form. Losartan possesses three indications: (1) treatment of hypertension; (2) to reduce the incidence of stroke in patients with both hypertension and left ventricular hypertrophy; and (3) treatment of diabetic nephropathy (*i.e.*, both hypercreatinemia [serum creatinine ≥ 1.3 mg/dL in females, ≥ 1.3 mg/dL in males ≤60 kg, and ≥ 1.5 mg/dL in males > 60 kg] and macro-albuminuria [urinary albumin-to-creatinine ratio ≥ 300 mg/g]) in patients with type II (i.e., non-insulin-dependent) diabetes mellitus and hypertension.[120] Several trials have assessed the efficacy of losartan in the treatment of heart failure. In the Evaluation of Losartan in the Elderly (ELITE) II trial, 3126 patients were randomized to receive captopril or losartan.[121] Study participants had clinical heart failure (New York Heart Association functional class II, III, or IV) and ejection fraction ≤ 40%. With mean follow-up of about 1.5 years, the hazard ratio of death due to any cause was 1.13 (95% confidence interval, 0.95-1.35) for losartan versus captopril, thereby admitting neither superiority nor inferiority. In the more recent Heart Failure End Point Evaluation of Angiotensin II Antagonist Losartan (HEAAL) trial, 3846 patients with similar heart

failure severity as in ELITE II were randomized to receive losartan at doses of either 50 mg daily or 150 mg daily.[122] Relative to the lower dose, the higher dose was associated with 10% lower risk of the composite endpoint of death or hospitalization for heart failure; the effect was modestly stronger for the component of hospitalization for heart failure. Although hyperkalemia, hypotension, and renal impairment occurred more frequently in patients who received the higher dose, treatment discontinuation rates were similar in the treatment groups.

Losartan is available in potencies of 25, 50 and 100 mg. Losartan is not a prodrug per se, as losartan itself antagonizes angiotensin II receptors. However, roughly 14% of an administered dose is metabolized by cytochrome P450 enzymes to an active metabolite (EXP3174) with an affinity to angiotensin II receptors that is roughly 10 times greater than losartan itself. The half-life of losartan is 2 hours, while the half-life of EXP3174 is between 6 and 9 hours. The drug is usually administered once per day, although twice-daily regimens may be prescribed for patients with hypertension and inadequate trough responses. Absorption is unaffected by the presence of food. Usual daily doses in patients with left ventricular hypertrophy or diabetic nephropathy are between 50 and 100 mg. Dose adjustment is unnecessary in patients with renal impairment, but is recommended in those with hepatic impairment. Dialysis does not clear losartan.

Valsartan

Valsartan was approved by the FDA on July 18, 2001. Valsartan is available in branded ("Diovan") or generic form. The agent is also available in combination with a calcium channel blocker, amlodipine, in branded ("Exforge") or generic form; a diuretic,

hydrchlorothiazide, in branded ("Diovan HCT") or generic form; or both amlodipine and hydrochlorothiazide, in branded ("Exforge HCT") or generic form. Valsartan has three indications: (1) treatment of hypertension; (2) treatment of HF; and (3) to reduce the incidence of death from cardiovascular causes in patients with an ejection fraction ≤ 40% by ventriculography or ≤ 35% by electrocardiography after acute myocardial infarction.[123] Efficacy of valsartan for treatment of heart failure was established by the Valsartan in Heart Failure (Val-HeFT) trial.[124] In that study, 5018 patients were randomized to received placebo or valsartan, in tandem with currently prescribed treatment. Study participants had clinical heart failure with ejection fraction ≤ 40% and left ventricular dilatation. Compared to placebo, valsartan had no effect on survival. However, valsartan was associated with 13% lower risk of the composite endpoint of death due to any cause, cardiac arrest with resuscitation, hospitalization for heart failure, or receipt of intravenous inotropic or vasodilator therapy for at least 4 hours; the reduction was dominated by 24% lower risk of hospitalization for heart failure. Valsartan is available in potencies of 40, 80, 160, and 320 mg. The drug has a half-life of roughly 9 hours. Valsartan may be administered either once or twice per day in patients with uncomplicated hypertension, but twice-daily regimens are recommended in patients with heart failure or depressed ejection fraction after acute myocardial infarction. The presence of food in the gastrointestinal tract does lower bioavailability, but this feature appears to be unimportant. Valsartan is primarily excreted by the liver, and dosage adjustment may be required in patients with severe hepatic impairment. Dialysis does not clear valsartan.