Optimal Pharmacotherapy for the Management of Heart Failure with Left Ventricular Systolic Dysfunction at Hospital Discharge

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CURRICULUM VITAE

Regina Catherine Grebla was born in Connecticut and was raised in Northwest Connecticut. She graduated from Canterbury School as a junior in 1997 and received a BSFS in Science, Technology and International Affairs with a concentration in International Security Studies from Georgetown University's School of Foreign Service in 2000. She holds a Master's degree in Government Administration from the University of Pennsylvania and a Master of Public Health in Epidemiology from Columbia University.

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DEDICATION

I dedicate this dissertation in memory of my uncle Roman Józef Kałuża (December 13, 1951 – December 27, 2010).

TABLE OF CONTENTS

LIST OF TABLES

Table Page

LIST OF FIGURES

Figure Page

INTRODUCTION

Chronic heart failure (HF) affects approximately 5.8 million Americans (2.6%) and 30-50% of patients die within one year of their first hospitalization for HF.[1-7] Current clinical practice guidelines for the management of HF with left ventricular systolic dysfunction (LVSD) are based on randomized controlled trial findings among stable, ambulatory HF patients. However, there is limited evidence about the safety and outcomes of HF therapies when used at hospital discharge among patients with LVSD, particularly among decompensated HF patients and HF patients with comorbid renal dysfunction, who are systematically excluded from HF therapy trials.[8] As a consequence, potentially beneficial HF therapies are used less often among these patients.[9, 10] This dissertation, therefore, focuses on identifying optimal pharmacotherapies for the management of HF with LVSD at discharge from hospitalization for acute HF decompensation. To address this objective, we performed three retrospective cohort studies examining the relationship between discharge HF pharmacotherapies and clinical outcomes among veterans with LVSD hospitalized for HF. Furthermore, we explored the relationship between discharge HF pharmacotherapies and clinical outcomes among subgroups of patients whose management is further complicated by two common comorbid conditions, renal dysfunction and cardiac arrhythmias.

In study one, we compared the effectiveness of three therapeutic strategies at hospital discharge for patients with HF and LVSD: individual angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) therapy, individual β-adrenergic receptor blocker (BB) therapy, and combined ACEI or ARB and BB therapy. Although clinical guidelines recommend combined ACEI/ARB and BB therapy for HF patients with LVSD at hospital discharge, no randomized controlled trial has examined the safety and efficacy of combined therapy at discharge, nor have there been trials among hospitalized HF patients to demonstrate combined therapy at discharge is more beneficial than either therapy individually. We therefore investigated this question among 19,303 patients hospitalized for HF with LVSD who received an ACEI/ARB, BB, or combined therapy at discharge using a three-way propensity matching study design. Our findings suggest combined therapy was optimal at discharge, as patients receiving combined therapy had fewer events during follow-up compared with patients receiving each therapy individually. However, receipt of a BB at hospital discharge without adjunctive ACEI/ARB therapy was associated with an elevated risk of short-term mortality when compared with both ACEI/ARB and combined therapy, suggesting that ACEI/ARB is potentially a better individual therapy at discharge for patients who cannot tolerate combined therapy.

Study two examined the use of ACEI/ARB at discharge among patients with both HF with LVSD and renal dysfunction, which included over half of patients in study one. The use of ACEIs and ARBs (renin-angiotensin system inhibitors) among patients with HF with LVSD and renal dysfunction has been associated with worsening renal function and detracts from the known therapeutic benefit of renin-angiotensin system inhibition in

HF. Furthermore, patients with moderate to severe renal dysfunction have been systematically excluded from HF clinical trials of ACEIs and ARBs, and there is limited evidence to compare the potential benefit of HF management with an ACEI or ARB with the expense of a further decline in renal function. To investigate this question, we studied 10,628 veterans hospitalized for HF with LVSD who had chronic kidney disease before admission. We examined the risk of mortality, rehospitalization for HF, and worsening renal function among 4,224 patients propensity-matched according to the receipt of ACEI or ARB therapy at discharge. The receipt of an ACEI or ARB at discharge was associated a meaningful reduction in the risk of HF rehospitalization regardless of severity of the patient's underlying renal dysfunction and was not associated with worsening renal function. These results suggest an ACEI or ARB at hospital discharge is optimal for HF patients with comorbid renal dysfunction.

In addition to renal dysfunction, cardiac arrhythmias were highly prevalent in our study population of patients hospitalized for HF with LVSD. For patients with both HF with LVSD and cardiac arrhythmias, the optimal management of HF at hospital discharge may require antiarrhythmic medications for pharmacological cardioversion. Non-dihydropyridine (DHP) calcium channel blockers (CCBs) are beneficial for the treatment of atrial arrhythmias; however, their safety in HF patients with LVSD is a concern. We therefore investigated whether the use of non-DHP CCBs (diltiazem and verapamil) at discharge among patients with both HF with LVSD and supraventricular tachyarrhythmias was associated with increased risk of mortality or rehospitalization for HF. We studied this question using a propensity-matching design among 8,732 patients hospitalized for HF with LVSD who had atrial fibrillation, atrial flutter, or paroxysmal

supraventricular tachyarrhythmia. The receipt of a non-DHP CCB at discharge was associated with lower mortality over 6 months and was not associated with HF rehospitalization. Our findings suggest the use of non-DHP CCBs at discharge is potentially beneficial in patients with both HF with LVSD and supraventricular tachyarrhythmias, among whom the majority received adjunctive ACEI or ARB therapy at discharge.

We have described these three studies in the following papers:

- Paper one: Choice of renin-angiotensin system inhibition, beta-blockade, or both at heart failure discharge affects short-term clinical outcomes;
- Paper two: Renin-angiotensin system inhibitor use at heart failure discharge improves clinical outcomes in patients with renal dysfunction;
- Paper three: The effect of treatment with non-dihydropyridine calcium channel blockers among patients with supraventricular tachyarrhythmias hospitalized for heart failure with left ventricular systolic dysfunction.

CHAPTER 1 :
CHOICE OF RENIN-ANGIOTENSIN SYSTEM INHIBITION, BETA-BLOCKADE, OR BOTH AT HEART FAILURE DISCHARGE AFFECTS SHORT-TERM CLINICAL OUTCOMES

Abstract

Context: Although clinical guidelines recommend combined angiotensin-converting-enzyme inhibitor (ACEI)/angiotensin-receptor blocker (ARB) and beta-blocker (BB) therapy for heart failure (HF) patients with reduced ejection fraction, little evidence is available to compare outcomes when these therapies are prescribed in combination, or individually, at hospital discharge.

Objective: To compare the effectiveness of an ACEI/ARB, a BB, or the combination thereof, at discharge from a HF hospitalization.

Design, Setting and Participants: We identified 21,849 patients hospitalized for HF with left ventricular ejection fraction < 40% at VA medical centers nationwide between 2003 and 2007. Patients who received a BB (11%), an ACEI/ARB (16%), or their combination (61%), were 1:1:1 propensity score matched. Differences in survival were evaluated by using the Kaplan-Meier method pair-wise log-rank tests. Cox proportional hazards regression models were used to estimate hazard ratios (HR) and corresponding 97.5% confidence intervals (CI) for the association between discharge therapy and study outcomes.

Main Outcome Measures: All-cause mortality and HF rehospitalization at 30 days and 6 months.

Results: Among 4,995 patients in our matched sample, receipt of a BB at discharge without an ACEI or ARB was associated with an increased hazard of all-cause mortality within 30 days compared with individual ACEI/ARB (HR: 1.62; 97.5% CI: 1.10, 2.40; log-rank P=0.009), and combined therapy (HR: 1.67; 97.5% CI: 1.13, 2.48; log-rank P=0.009). No significant differences in survival from all-cause mortality were found

between either individual therapy and combined therapy at discharge within 6 months. No significant association between the studied HF therapies at discharge and risk of HF rehospitalization was found.

Conclusions: In three-way propensity-matched analyses of veterans hospitalized with decompensated HF and reduced ejection fraction, receipt of a BB at hospital discharge without adjunctive ACEI/ARB therapy was associated with an elevated risk of short-term mortality when compared with ACEI/ARB and combined therapy.

Introduction

Heart failure (HF) is a leading cause of hospital admissions in the United States and other industrialized nations, and the prevalence of HF and its associated health care costs are projected to escalate.[5, 11, 12] Current clinical practice guidelines for patients hospitalized for HF with reduced left ventricular ejection fraction (LVEF) recommend the initiation of both angiotensin-converting-enzyme inhibitors (ACEIs), or angiotensin-receptor blockers (ARBs) for patients who cannot tolerate an ACEI, and β-Blockers (BBs) prior to discharge.[12, 13] No randomized controlled trial, however, has examined the safety and efficacy of combined therapy at discharge among a population of patients hospitalized for HF, nor have there been trials among hospitalized HF patients demonstrating that combined therapy at discharge is more beneficial than either therapy individually.

Recent studies have suggested that up to half of HF patients continue to receive either an ACEI/ARB or a BB at discharge, not in combination.[14, 15] For patients who cannot tolerate combined therapy, there is a paucity of information about which of these

therapies is optimal at discharge, particularly among individuals with potential treatment contraindications, such as renal insufficiency, excluded from clinical trial populations. As the number of HF patients is anticipated to increase, identifying optimal therapeutic strategies following HF hospitalization is of growing importance. The Veterans Affairs (VA) Health Care System affords a unique opportunity to explore the relationship between discharge HF therapy and clinical outcomes among a general HF population by providing comprehensive information about medication utilization, hospitalization within and outside the VA system, and mortality. Using a three-way propensity matching design, we studied the association between the receipt of an ACEI/ARB, a BB, or the combination thereof, at discharge from a HF hospitalization and all-cause mortality and HF rehospitalization among VA patients with LVEF <40% between 2003 and 2007.

Methods

Study Design

Veterans age 18 years or older who were hospitalized for HF with LVEF <40% at a VA medical center between January 15, 2003 and November 15, 2007 were identified using data from the VA External Peer Review Program (EPRP). The VA's Office of Quality and Performance contracts trained medical reviewers to abstract charts from a random nationwide sample of veterans in the EPRP to evaluate the quality of care delivered by VA facilities according to evidence-based performance measures. The EPRP sampling frame includes all VA beneficiaries with at least two years of continuous enrollment and who had at least one VA outpatient visit or hospitalization in the year before assessment. [16, 17]

Participants

Patients were identified using three EPRP performance measures for ACEI/ARB use among HF patients with LVEF <40%. To be eligible, patients must have a principal discharge diagnosis of HF and chart documentation of LVEF <40% or a narrative description of moderate or severe left ventricular systolic dysfunction. Exclusion criteria for these measures included allergy to both an ACEI and ARB, moderate or severe renal artery stenosis, participation in a clinical trial, and transfer to another hospital or hospice care.[18] For patients with multiple EPRP assessments (7,203/32,566; 22%), we used the earliest inpatient assessment during the study period. Because the EPRP data does not specify the hospitalization assessed, we selected the closest VA HF hospitalization up to three months before or one month after their EPRP assessment date. We defined hospitalization for HF using *International Classification of Diseases, Ninth Revision* [*ICD-9-CM*] codes in the patient's primary diagnosis: 428.0 (congestive HF, unspecified), 428.1 (left HF); 428.2 (systolic HF) which is unspecified (428.20), acute (428.21), chronic (428.22), or acute or chronic (428.23); 428.3 (diastolic HF) which is unspecified (428.30), acute (428.31), chronic (428.32), or acute or chronic (428.33); 428.4 (combined systolic and diastolic HF), which is unspecified (428.40), acute (428.41), chronic (428.42), or acute or chronic (428.43); 428.9 (HF, unspecified); 398.91 (rheumatic HF); 402.01, 402.11, or 402.91 (hypertensive heart disease with HF); and 404.01, 404.03, 404.11, 404.13, 404.91, or 404.93 (hypertensive heart disease and chronic kidney disease with HF). Same-day readmissions for HF were treated as a single hospital stay. Patients who did not fill a prescription for an ACEI, ARB or BB prior to the index date (n=2,546;

12%) were excluded from the final sample. A flow diagram of study inclusion and exclusion criteria is illustrated in **Figure 1-1**.

Sources of Data

Information about inpatient and outpatient visits was obtained from the VA National Patient Care Database. Laboratory results and medication information were obtained from VA Decision Support System records. [19, 20] To account for use of Medicare services during the study period, we used data from the VA/CMS Data for Research project.[21] We ascertained a patient's vital status by combining the VA Beneficiary Identification and Record Locator Subsystem dataset with VA/CMS data linked to Medicare's Enrollment Database.

Exposure Definitions

We defined exposure to ACEI/ARB or BB as the receipt of these medications on the final day of the patient's index hospitalization or by an outpatient fill within 7 days of discharge. [22, 23] For the primary analyses, we assigned patients to one of three treatment categories according to the patient's exposure: (1) BB; (2) ACEI and/or ARB; (3) combined therapy with an ACEI and/or ARB and a BB. Each treatment category was compared to combined therapy, which was the most widely prescribed treatment.

Outcome Definitions

The primary outcome of this study is all-cause mortality. The secondary outcome was rehospitalization for HF identified by the VA or Medicare datasets. Outcomes were estimated at 30 days and 6 months. The index date of observation for all patients was 7 days after discharge from the patient's index HF hospitalization.

Patient Characteristics/Covariates

Sociodemographic characteristics included the presence of any service-connected disability, medication copayments using the VA means test indicator, and marital status. We used the most frequent value of self-identified patient race from inpatient and outpatient records and categorized patients as white, black (including Non-Hispanic Black or African American), or other (including Hispanic or Latino, American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander).[24] For patients whose race could not be determined from the VA datasets (n=779), we substituted race, when available, from the VA/CMS dataset. We assigned the VA Medical Center that provided treatment to U.S. Census Regions. We also examined the number of hospitalizations during the 6 months prior to the index hospitalization, length of stay, and long-term care admissions up to 6 months before admission and during follow-up. We used VA/CMS Medicare outpatient claims to identify whether patients sought non-VA care during the study period.

We obtained laboratory, vital sign information, and demographic characteristics reported at admission. Body mass index (BMI) was calculated from the patient's weight up to 6 months before admission and height recorded at any time. We examined two-

year history of HF hospitalization, coronary artery disease, acute myocardial infarction (AMI), angina, percutaneous coronary intervention (PCI), coronary bypass grafting (CABG), atrial fibrillation, and the presence of a pacemaker or implantable defibrillator. We also examined concomitant use of other HF therapies at discharge. Prior BB and prior ACEI or ARB use was defined as the receipt of these medications in the 90 days before admission.

We assessed patients for the presence of potential contraindications to treatment with BBs or with ACEIs. Potential contraindications to BBs included bradycardia, advanced atrioventricular block without a pacemaker, hypotension, broncheospastic respiratory disease, and co-morbid chronic obstructive pulmonary disease during the two years before the index admission; and pulse < 60 beats/minute, systolic blood pressure < 85 mmHg, and concomitant use of chronic respiratory medications at admission.[25] Potential contraindications to ACEIs included pregnancy within one year of the index admission, co-morbid renal failure, renal artery stenosis, angioedema, and hypotension; and systolic blood pressure < 85mmHg, and serum potassium > 5.5 mEq/L, and creatinine clearance < 30 mL/min at admission.[25]

Co-morbid conditions were identified using 28 revised conditions from the Elixhauser Comorbidity Index software available on the Agency for Healthcare Research and Quality (AHRQ) website and based upon VA and Medicare inpatient and outpatient claims from the two years prior to index hospitalization. We added Quan's modification to include cardiac arrhythmias, a common secondary diagnosis among HF patients, and excluded co-morbid HF.[26] The sum of comorbidities, which included a patient's total of the 29 conditions, was included as an additional covariate.

Statistical Analyses

Missing values for potential confounders including hematocrit (6.4%), serum creatinine (7.0%), BMI (4.0%), and sodium, potassium, systolic blood pressure, diastolic blood pressure, and pulse, which were missing in 1-2% of the overall sample, were imputed using mean values from 10 imputed datasets. Missing values of hematocrit were estimated with hemoglobin values (hemoglobin x 3) when available.[27] Baseline characteristics before matching were compared using chi-square tests for categorical variables and t-tests for continuous variables.

To address between-patient variation not adequately controlled with standard multivariable approaches, we used propensity score methods.[28-30] We estimated individual propensity scores for BB versus combined therapy and for ACEI/ARB versus combined therapy using a nonparsimonious multinomial logistic regression model which included all baseline characteristics reported in **Table 1-1**.[31-34] We created matched sets of triplets using a 1:1:1 nearest-neighbor matching algorithm with combination therapy as the common referent.[35, 36] To assess the success of matching in balancing potential confounders, we calculated standardized differences between each individual therapy and combined therapy before and after matching.[37] A standardized difference <0.10 suggests similar distribution among groups.[38, 39]

Kaplan-Meier curves were used to estimate the cumulative probability of survival from all-cause mortality and HF rehospitalization according to HF therapy. Differences in survival among the three treatment groups were compared using the log-rank test with a Bonferroni-adjustment for multiple comparisons. To control for type I error introduced

by multiple endpoints (30 days and 6 months) in our study, we set statistical significance for the log-rank test at 0.025 (0.05/2).[40] Survival time was measured as the number of days between the index date until the outcome of interest or May 15, 2008.

Cox proportional hazards models were used to estimate hazard ratios (HRs) for all outcomes using three models: ACEI/ARB versus combined therapy, BB versus combined therapy, and ACEI/ARB versus BB. We estimated 97.5% CIs to approximate simultaneous 95% CIs to accommodate multiple testing. We evaluated the appropriateness of the proportional hazards assumption for each model using Martingale residuals and by visual inspection of negative log-log plots. As a sensitivity analysis, we examined whether the association between HF therapy and all-cause mortality differed when censoring patients who were rehospitalized for HF during the study period, who were more likely to discontinue or change medications during subsequent HF hospitalizations.

All analyses were performed with SAS 9.2 (SAS Institute, Cary, NC). The Providence VA Medical Center institutional review board approved the study protocol.

Results

A total of 19,303 veterans hospitalized for HF at 120 VA medical centers nationwide were identified **(Figure 1-1)**. At discharge, the majority of patients received combined therapy (61%), followed by ACEI/ARB (16%), and BB (11%) therapy individually. The baseline characteristics of patients in each treatment group before matching are presented in **Table 1-1**. Patients who received a BB without an ACEI/ARB were more often white, had more comorbid conditions, and were more likely to have a

history of cardiovascular disease, whereas patients who received an ACEI/ARB without a BB had higher eGFR and were more likely to receive diuretics or digoxin for HF at discharge. Compared with patients treated with combined therapy, patients who received BB therapy were older, had lower estimated kidney function, and were twice as likely to receive hydralazine at discharge ($P<0.001$ for all comparisons). In contrast, patients treated with an ACEI/ARB were less likely than combined therapy patients to have a history of coronary artery disease, AMI, hypertension, or to receive nitrates at discharge. A larger proportion of patients treated at VA medical centers in the Midwest received a BB as an individual therapy compared with ACEI/ARB (26% vs. 19%; $P<0.001$). After 6 months of follow-up, 2,952 patients (15%) in the unmatched cohort died and 7,289 (38%) were rehospitalized for HF.

We successfully 1:1:1 matched 66% (1,665 / 2,505) of patients receiving a BB individually to ACEI/ARB patients and a common combined therapy control for a total of 4,995 propensity-matched patients. Baseline characteristics of the propensity-matched sample are shown in **Table 1-2**. Standardized differences for all covariates were <0.10, indicating the balance of baseline covariates improved after matching. The mean age of matched patients was 70.3±11.6 years. The majority of patients were white (71%), male (99%), had a history of coronary artery disease (75%), and received a diuretic at discharge (85%). A quarter of patients in the propensity-matched sample were previously hospitalized for HF, and half had been treated with an ACEI/ARB or BB 90 days before admission. Many treated patients had potential contraindications to ACEIs (38%) or BBs (62%).

Association with Outcomes

Figures 1-2 and 1-3 presents Kaplan-Meier estimates of the cumulative incidence of all-cause mortality and HF hospitalization according to matched treatment group. After 30 days, 87 patients (5.2%) who received individual BB therapy died, compared with 54 patients (3.2%) who received ACEI/ARB therapy (HR 1.62; 97.5% CI: 1.10, 2.40; log-rank P=0.009), or with patients who received combined therapy (54 patients, 3.2%; HR: 1.67; 97.5% CI: 1.13, 2.48; log-rank P=0.009). **(Table 1-3 and Figure 1-2)** There was no statistically-significant difference in survival from all-cause mortality between ACEI/ARB and combined therapy recipients at 30 days. After 6 months, a similar number of deaths occurred among those who had received ACEI/ARB or BB individually (19.0% versus 19.3%; log-rank P=1.00). Although fewer patients treated with combined therapy died after 6 months (266 patients, 16%), the differences in survival between combined therapy and BB therapy (HR: 1.28; 97.5% CI: 1.05, 1.55; log-rank P=0.030) or ACEI/ARB therapy (HR: 1.20; 97.5% CI: 0.99, 1.45; log-rank P=0.081) were not statistically-significant according to the log-rank test after adjusting for multiple comparisons.

Treatment at hospital discharge with an ACEI/ARB, a BB, or their combination was not associated with HF rehospitalization at 30 days or at 6 months among patients in our study. **(Table 1-3 and Figure 1-3)** A violation of the proportional hazards assumption was detected for 6-month HF rehospitalization in the ACEI/ARB versus combined therapy comparison (p=0.0475); however, the addition of an interaction between treatment and survival time dichotomized at the point of convergence to the model was not statistically-significant (P=0.1724).

Sensitivity analyses to examine whether the association between HF therapy and all-cause mortality differed among patients rehospitalized for HF during follow-up showed a consistent increased risk of mortality at 30 days among patients treated with individual BB therapy compared with individual ACEI/ARB therapy (HR: 1.56; 97.5% CI: 0.997, 2.44; log-rank P=0.021) and combined therapy (HR: 1.74; 97.5% CI: 1.08, 2.80; log-rank P=0.014) **(Table 1-4 and Figure 1-4)**. However, we did not find differences in survival from all-cause mortality at 6 months between discharge HF therapies (log-rank P>0.025 for all comparisons).

Comment

In this large observational study of veterans hospitalized for acute HF with reduced LVEF, we found the receipt of a BB at discharge without an ACEI/ARB was associated with a 60% higher short-term risk of mortality compared with both individual ACEI/ARB therapy and combined therapy. This finding is especially relevant when considering a sizable proportion of patients received individual BB therapy at discharge, and who were among 40% of patients in our original sample who did not receive combined therapy at discharge. After 6 months, however, survival from all-cause mortality was not significantly different between patients receiving either individual therapy. Although combined therapy recipients had lower rates of all-cause mortality within 6 months, pairwise comparisons of survival with between combined and individual therapy recipients did not reach statistical significance. In addition, we did not find a difference in rehospitalization for HF within 30 days or 6 months between discharge therapies.

Three studies have performed head-to-head comparisons of ACEI and BB individually to examine whether the order of initiation of these therapies in stable outpatients was associated with different clinical outcomes. The CARMEN (Carvedilol ACE-Inhibitor Remodelling Mild CHF Evaluation) trial compared enalapril, carvedilol, and their combination among 572 stable HF patients with LVEF <40% and observed a non-significant beneficial effect of combined therapy on hospitalization.[41] A single-center study among 78 newly diagnosed HF outpatients with LVEF <40% compared their order of initiation and found initiation with a BB had a more favorable effect on functional capacity.[42] More recently, the Cardiac Insufficiency Bisoprolol (CIBIS) III trial found no statistically-significant difference in the combined endpoint of all-cause mortality and hospitalization for any reason among 1,010 stable HF patients with LVEF ≤35% treated with either an ACEI or a BB for 6 months; however, individual BB therapy was associated with a lower risk of sudden death and higher risk of HF rehospitalization.[43, 44]

Our study included a sicker population of patients who were hospitalized for HF, a setting where BB therapy has not been studied previously in the absence of background ACEI/ARB in randomized controlled trials. It is unlikely that our findings of a lower mortality risk among patients receiving an ACEI/ARB compared with those who received a BB can be explained by differences in study populations alone. It is likely that the beneficial early unloading effect of renin-angiotensin inhibition on the left ventricle may manifest in better short-term outcomes among patients experiencing HF decompensation.[45] The beneficial anti-remodelling effects of BB therapy have been shown to be greater than ACEI therapy, but the clinical benefit of β-adrenergic blockade

is not observed as quickly as with renin-angiotensin inhibition.[46] A study comparing the time until a clinical benefit was realized among stable HF patients enrolled in major ACEI and BB trials found that patients benefited from ACEI therapy almost immediately, as evidenced by a divergence of survival curves within a month of initiation, whereas 2 to 4 months elapsed before a similar survival benefit was observed for BBs.[47] Similar time trends in mortality risks were observed in our study population and may explain the trend towards additional reduction in mortality within 6 months among combined therapy recipients that was not observed at 30 days.

Despite our results, individual BB therapy should not be interpreted as harmful in itself since we did not compare outcomes against patients who did not receive any of the studied treatments at discharge. Indeed, crude mortality was similar among patients who did not receive either an ACEI/ARB or BB at discharge compared with patients who received a BB at discharge at 30 days (5.6% vs. 5.5%), and higher at 6 months against patients who received neither therapy (23.5% vs. 21.4%) in our unmatched study population (data not shown).

The strengths of our study included the ability to perform a head-to-head comparison of ACEI/ARB therapy and BB therapy individually for the treatment of HF among a large, nationally-representative, sample of veterans for whom we had comprehensive information on clinical measures and outcomes in both the VA and Medicare. Our study included those with contraindications to these therapies who were traditionally excluded from clinical trials. The three-way propensity score matching algorithm enabled us to select patients who were equally likely to receive any of the HF therapies at discharge and approach the challenge of confounding by indication.

Our study also has several limitations. Because we did not have access to all patient records specifying discharge medications, we approximated exposure at discharge by considering medications used on the last inpatient day in addition to the possibility that patients might fill prescriptions for discharge medications on an outpatient basis. Although earlier studies assessing this concern using claims data found the majority of patients filled discharge medications during this timeframe[22], there remains the possibility of non-differential exposure misclassification in our study. Although we were able to identify non-VA hospitalizations using VA/CMS data, we could not fully capture non-VA utilization among VA patients without Medicare. Indeed, only 59% of patients with qualifying VA HF hospitalizations (14,397/ 24,364) also had an inpatient or outpatient claim in the VA/CMS dataset and may have led us to underestimate HF rehospitalization and non-VA utilization. Finally, the generalizability of our findings is limited by the composition of predominantly male study population; however, our study population was more racially diverse and included patients older than those included in major HF clinical trials.

Conclusion

In three-way propensity-matched analyses of veterans hospitalized with decompensated HF and reduced ejection fraction, receipt of a BB at hospital discharge without an ACEI/ARB was associated with an elevated risk of mortality at 30 days, but not at 6 months, when compared with ACEI/ARB or combined ACEI/ARB and BB therapy. In addition to supporting the use of combined therapy at discharge, our study

suggests that ACEIs/ARBs are potentially a better individual therapy compared with BBs at discharge for patients who cannot tolerate combined therapy.

Tables and Figures

Table 1-1. Baseline Demographic and Clinical Characteristics of Overall Study Cohort by Treatment Group (n=19,303)

Characteristic	BB (N=2,505)	ACEI/ARB (N=3,535)	Combined (N= 13,263)	Overall (N=19,303)	P-values[a] BB vs. Combined	ACEI/ARB vs. Combined	BB vs. ACEI/ARB
Age at index date, years, mean (SD)	70.5 (11.3)	69.8 (12.1)	68 (11.7)	68.6 (11.8)	<.0001	<.0001	0.0228
Female sex, %	1.3	1.2	1.1	1.2	0.5515	0.6005	0.9104
Race, %[b]							
White	71.1	65.4	67.7	67.7	<.0001	0.0291	<.0001
Black	21.1	26.8	25.1	24.9			
Other	7.3	7.2	6.4	6.6			
Married, %	48.0	43.3	42.5	43.3	<.0001	0.3454	0.0006
Any service-connected disability, %	30.6	30.2	29.7	29.9	0.3406	0.5092	0.7528
Required copayment, %	10.2	9.5	10.7	10.4	0.4959	0.0482	0.3772
VAMC Census Region, %							
Northeast	10.9	11.9	13.5	12.9	<.0001	<.0001	<.0001
Midwest	26.3	19.1	22.5	22.4			
South	42.8	48.7	44.9	45.3			
West	18.6	18.1	17.6	17.9			
Outside Census Regions	1.5	2.1	1.5	1.6			
Fiscal year of index admission, mean	2006	2005	2005	2005	<.0001	<.0001	<.0001
Length of Stay, index hospitalization, days, mean (SD)	6.1 (6.7)	5.3 (5.3)	5.3 (4.9)	5.4 (5.3)	<.0001	0.4133	<.0001
Length of Stay during prior 6 months, days, mean (SD)	12.7 (15)	11.6 (14.6)	11.1 (13.2)	11.5 (13.7)	0.0002	0.2612	0.0476
Inpatient Stays during prior 6 months, mean (SD)	1.0 (1.4)	0.7 (1.2)	0.8 (1.2)	0.8 (1.2)	<.0001	0.4846	<.0001
HF Inpatient Stays during prior 6 months, mean (SD)	0.2 (0.6)	0.1 (0.5)	0.1 (0.4)	0.1 (0.5)	<.0001	0.1441	0.0001

Long-term care admissions, %	15.6	12.8	11.8	12.5		<.0001	0.1316	0.0019
Use of non-VA outpatient services, % [f]	25.6	22.1	20.7	21.6		<.0001	0.0764	0.0018
Prior BB use, %	57.8	28.6	54.2	50.0		0.0011	<.0001	<.0001
Prior ACEI/ARB use, %	42.2	50.2	55.1	52.6		<.0001	<.0001	<.0001
Potential contraindications to ACEIs, % [d]	51.7	27.0	28.9	31.5		<.0001	0.0306	<.0001
Potential contraindications to BBs, % [e]	63.6	60.6	56.2	57.9		<.0001	<.0001	0.0166
History of cardiovascular disease, %								
Previous HF hospitalization	28.4	23.7	22.1	23.2		<.0001	0.0568	<.0001
Coronary artery disease	78.2	65.3	72.7	72.0		<.0001	<.0001	<.0001
History of AMI	48.8	36.7	41.7	41.7		<.0001	<.0001	<.0001
Angina	13.0	8.7	10.3	10.4		<.0001	0.005	<.0001
Percutaneous Intervention	11.5	7.8	10.5	10.1		0.1524	<.0001	<.0001
CABG	2.0	1.4	1.6	1.6		0.0912	0.4331	0.0512
Pacemaker/defibrillator, %	24.6	16.6	19.8	19.9		<.0001	<.0001	<.0001
Atrial fibrillation, %	40.1	33.2	36.2	36.2		0.0002	0.0009	<.0001
Concomitant heart failure therapy, %								
Calcium Channel Blockers	11.2	13.2	10.4	11.0		0.2333	<.0001	0.0189
Digoxin	27.9	35.1	37.2	35.6		<.0001	0.0192	<.0001
Diuretics	81.5	88.4	92.4	90.3		<.0001	<.0001	<.0001
Hydralazine	22.2	5.9	8.7	9.9		<.0001	<.0001	<.0001
Nitrates	42.4	26.5	35.3	34.6		<.0001	<.0001	<.0001
Laboratory Values, mean (SD)								
Hematocrit, %	36.6 (5.9)	38 (5.7)	38.3 (5.7)	38.1 (5.7)		<.0001	0.0025	<.0001
Mean blood pressure, mmHg	92.6 (16.6)	93.8 (16.8)	95.8 (17.2)	95 (17.1)		<.0001	<.0001	0.0057
Pulse, beats/minute	82.6 (18.2)	84.1 (18.1)	83.8 (18.4)	83.7 (18.3)		0.0032	0.3718	0.0017
eGFR, ml/min/1.73m²	49.4 (23.4)	61.7 (22.4)	61.6 (22.6)	60.0 (23.0)		<.0001	0.8118	<.0001
Kidney disease, %								
Mild or none, (eGFR >60ml/min/1.73m²)	30.3	50.8	50.3	47.8		<.0001	0.6111	<.0001
Moderate, (eGFR 30-59 ml/min/1.73m²)	46.0	41.9	42.8	43.0				
Severe, (eGFR <30 ml/min/1.73m²)	23.6	7.2	6.9	9.2				
Sodium, mEq/L	137.6 (4.2)	137.9 (4.2)	137.8 (4.1)	137.8 (4.1)		0.0237	0.8688	0.0499
Potassium, mEq/L	4.1 (0.6)	4 (0.6)	4 (0.6)	4 (0.6)		<.0001	0.9562	<.0001

	BMI, kg/m²	29.1 (6.8)	28.6 (6.8)	29.6 (6.8)	29.3 (6.8)		0.0018	<.0001	0.0032
Number of comorbid conditions, mean (SD)[c]		5.7 (2.6)	4.9 (2.4)	5.0 (2.5)	5.1 (2.5)		<.0001	0.1193	<.0001
Comorbid conditions, %[c]									
	Cardiac arrhythmias	26.6	20.8	22.6	22.8		<.0001	0.0208	<.0001
	Valvular disease	29.6	25.5	26.4	26.7		0.0010	0.2861	0.0005
	Pulmonary circulation disorders	13.5	11.9	12.5	12.5		0.1513	0.3258	0.0564
	Peripheral vascular disease	28.4	23.0	22.5	23.4		<.0001	0.5404	<.0001
	Hypertension	89.9	84.9	88.4	88.0		0.0312	<.0001	<.0001
	Paralysis	5.0	4.1	3.8	4.0		0.0053	0.5008	0.079
	Other neurological	6.5	6.8	6.2	6.3		0.5284	0.1627	0.6341
	Chronic pulmonary disease	48.0	47.6	43.1	44.6		<.0001	<.0001	0.7508
	Diabetes (uncomplicated)	26.0	26.3	27.7	27.2		0.0806	0.11	0.7614
	Diabetes (complicated)	27.8	20.9	23.3	23.4		<.0001	0.0022	<.0001
	Hypothyroidism	13.0	11.1	9.8	10.5		<.0001	0.0234	0.028
	Renal failure	38.5	15.3	19.5	21.2		<.0001	<.0001	<.0001
	Liver disease	5.6	6.5	5.7	5.9		0.8409	0.0713	0.1491
	Peptic ulcer disease	0.2	0.4	0.2	0.2		0.8505	0.1147	0.2375
	AIDS/HIV	0.3	0.7	0.6	0.5		0.1379	0.4824	0.0759
	Lymphoma	1.1	0.9	1.2	1.1		0.8522	0.2518	0.4805
	Metastatic cancer	1.2	1.3	1.1	1.2		0.7734	0.4836	0.7944
	Solid tumor without metastasis	12.7	10.8	10.2	10.6		0.0002	0.3145	0.0224
	Rheumatoid arthritis/collagen vascular diseases	2.6	2.4	2.5	2.5		0.7171	0.6479	0.5248
	Coagulopathy	12.4	9.3	9.6	9.9		<.0001	0.5298	0.0001
	Obesity	17.8	14.9	19.0	18.1		0.1501	<.0001	0.0023
	Weight loss	7.5	6.8	6.9	7.0		0.3495	0.7027	0.2924
	Fluid and electrolyte disorders	42.7	31.7	31.2	32.8		<.0001	0.5327	<.0001
	Blood loss anemia	3.5	1.9	2.2	2.3		<.0001	0.3498	<.0001
	Deficiency anemias	42.7	33.3	32.4	33.9		<.0001	0.2929	<.0001
	Alcohol abuse	10.1	14.3	12.7	12.6		0.0004	0.0094	<.0001
	Drug abuse	4.7	10.2	7.2	7.4		<.0001	<.0001	<.0001
	Psychoses	9.2	9.8	9.5	9.5		0.7226	0.5069	0.439

	Depression	19.0	17.7	18.1	18.1		0.2575	0.6384	0.1998

Abbreviations: HF = heart failure; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta blocker; combined therapy = ACEI or ARB and BB; CABG = coronary artery bypass grafting; AMI = acute myocardial infarction; eGFR = estimated glomerular filtration rate according to the CKD-EPI equation; VAMC = VA Medical Center; SD= standard deviation

[a] P-values reported for t-tests of continuous variables and chi-square tests for categorical variables for each two-group comparison

[b] Race values do not add up to 100% due to unknown race (<1%)

[c] Comorbid conditions include a total of 29 Elixhauser comorbid conditions and cardiac arrhythmias

[d] Potential contraindications to ACEIs include: pregnancy, renal failure, renal artery stenosis, angioedema, hypotension, systolic blood pressure < 85mmHg, serum potassium > 5.5 mEq/L, or creatinine clearance < 30 mL/min.

[e] Potential contraindications to BBs include: bradycardia, advanced atrioventricular block without a pacemaker, hypotension, asthma, broncheostasis, chronic obstructive pulmonary disease, pulse < 60 bpm, systolic blood pressure < 85 mmHg, or concomitant use of chronic respiratory medications at the time of index hospitalization

[f] Use of non-VA services = at least one Medicare outpatient visit in the year following the patient's index date

Table 1-2. Baseline Demographic and Clinical Characteristics of Propensity-Matched Study Cohort by Treatment Group (n=4,995)

Characteristic	BB (N= 1,665)	ACEI/ARB (N= 1,665)	Combined (N= 1,665)	Overall (N= 4,995)	Standard Difference [a] ACEI/ARB	Standard Difference [a] BB
Age at index date, years, mean (SD)	70.1 (11.6)	70.5 (11.5)	70.4 (11.7)	70.3 (11.6)	0.005	0.029
Female sex, %	1.3	1.3	1.7	1.4	0.040	0.044
Race, %[b]						
White	69.9	71.4	70.1	70.5	0.028	0.004
Black	22.1	21.4	22.1	21.9	0.016	0.000
Other	7.5	6.9	7.2	7.2	0.014	0.009
Married, %	47.1	46.5	44.5	46.0	0.040	0.052
Any service-connected disability, %	29.9	31.1	32.7	31.2	0.034	0.060
Required copayment, %	10.0	9.4	9.6	9.7	0.006	0.016
VAMC Census Region, %						
Northeast	10.3	11.4	13.0	11.6	0.051	0.086
Midwest	23.9	21.9	22.7	22.8	0.020	0.028
South	45.3	46.0	44.3	45.2	0.033	0.019
West	18.6	19.2	18.6	18.8	0.015	0.002
Outside Census Regions	1.9	1.7	1.4	1.7	0.024	0.042
Fiscal year of index admission, mean	2005	2005	2005	2005	0.006	0.001
Length of Stay, index hospitalization, days, mean (SD)	5.6 (5.3)	5.7 (6.1)	5.5 (5.0)	5.6 (5.5)	0.031	0.010
Length of Stay during prior 6 months, days, mean (SD)	12.4 (15.0)	12.6 (16.7)	12 (13.1)	12.3 (15.0)	0.004	0.009
Inpatient Stays during prior 6 months, mean (SD)	0.9 (1.3)	0.9 (1.3)	0.9 (1.3)	0.9 (1.3)	0.016	0.007
HF Inpatient Stays during prior 6 months, mean (SD)	0.2 (0.5)	0.2 (0.5)	0.2 (0.5)	0.2 (0.5)	0.021	0.008
Long-term care admissions, %	14.4	13.8	13.6	13.9	0.005	0.021
Use of non-VA outpatient services, % [f]	23.7	22.7	24.4	23.6	0.040	0.017
Prior BB use, %	48.5	48.2	47.7	48.1	0.011	0.016
Prior ACEI/ARB use, %	49.7	45.5	48.1	47.8	0.052	0.031
Potential contraindications to ACEIs, % [d]	38.2	37.0	39.2	38.1	0.046	0.021
Potential contraindications to BBs, % [e]	62.2	61.4	62.0	61.9	0.014	0.004

History of cardiovascular disease, %								
	Previous HF hospitalization	25.7	24.6	28.4	26.2		0.084	0.061
	Coronary artery disease	75.0	74.6	73.9	74.5		0.016	0.026
	History of AMI	45.5	45.1	44.4	45.0		0.014	0.023
	Angina	11.8	10.7	12.2	11.6		0.047	0.013
	Percutaneous Intervention	10.0	10.3	9.0	9.8		0.047	0.035
	CABG	1.7	1.6	2.6	2.0		0.075	0.066
	Pacemaker/defibrillator, %	21.5	21.3	21.7	21.5		0.009	0.004
	Atrial fibrillation, %	38.4	37.8	38.4	38.2		0.011	0.000
Concomitant heart failure therapy, %								
	Calcium Channel Blockers	10.6	10.8	12.2	11.2		0.045	0.049
	Digoxin	29.6	28.4	29.7	29.2		0.030	0.004
	Diuretics	83.8	84.6	85.1	84.5		0.013	0.035
	Hydralazine	9.8	10.3	11.1	10.4		0.027	0.043
	Nitrates	32.4	32.4	34.2	33.0		0.038	0.038
Laboratory Values, mean (SD)								
	Hematocrit, %	37.5 (5.7)	37.5 (5.7)	37.4 (5.8)	37.5 (5.7)		0.025	0.011
	Mean blood pressure, mmHg	93.0 (16.6)	92.7(16.5)	93.6 (17.4)	93.1 (16.9)		0.050	0.036
	Pulse, beats/minute	83.3 (18.5)	82.7 (18.4)	83.0 (18.5)	83.0 (18.5)		0.017	0.017
	eGFR, ml/min/1.73m²	55.8 (23.0)	56.6 (21.7)	55.3 (21.5)	55.9 (22.1)		0.061	0.024
	Kidney disease, %							
	Mild or none, (eGFR >60 ml/min/1.73m²)	40.5	41.4	39.1	40.4		0.048	0.029
	Moderate, (eGFR 30-59 ml/min/1.73m²)	45.6	47.6	49.5	47.6		0.038	0.078
	Severe, (eGFR <30 ml/min/1.73m²)	13.9	11.0	11.4	12.1		0.013	0.074
	Sodium, mEq/L	137.7 (4.2)	137.7 (4.2)	137.6 (4.1)	137.7 (4.2)		0.017	0.015
	Potassium, mEq/L	4.1 (0.6)	4.0 (0.6)	4.1 (0.6)	4.1 (0.6)		0.014	0.009
	BMI, kg/m²	28.9 (6.8)	29.1 (7.0)	29.1 (6.6)	29 (6.8)		0.004	0.023
Number of comorbid conditions, mean (SD)[c]		5.3 (2.5)	5.2 (2.5)	5.4 (2.6)	5.3 (2.5)		0.059	0.037
Comorbid conditions, %[c]								
	Cardiac arrhythmias	24.0	24.9	24.9	24.6		0.000	0.021
	Valvular disease	28.6	27.7	28.2	28.2		0.011	0.009
	Pulmonary circulation disorders	12.7	12.2	13.0	12.6		0.024	0.009

	Peripheral vascular disease	26.4	25.4	26.8	26.2		0.033	0.010
	Hypertension	88.0	88.1	87.8	88.0		0.007	0.006
	Paralysis	4.3	4.8	4.2	4.4		0.029	0.006
	Other neurological	6.3	5.9	6.6	6.3		0.027	0.010
	Chronic pulmonary disease	46.4	46.0	46.7	46.4		0.014	0.007
	Diabetes (uncomplicated)	26.4	26.7	26.8	26.6		0.001	0.010
	Diabetes (complicated)	24.3	24.7	25.1	24.7		0.007	0.017
	Hypothyroidism	12.1	11.7	12.0	11.9		0.007	0.006
	Renal failure	24.6	23.5	25.5	24.5		0.045	0.021
	Liver disease	5.1	6.1	5.5	5.6		0.026	0.021
	Peptic ulcer disease	0.2	0.4	0.3	0.3		0.010	0.012
	AIDS/HIV	0.5	0.6	0.4	0.5		0.025	0.009
	Lymphoma	1.1	0.8	1.4	1.1		0.057	0.027
	Metastatic cancer	1.2	0.9	1.9	1.3		0.087	0.058
	Solid tumor without metastasis	12.1	10.8	12.3	11.7		0.045	0.004
	Rheumatoid arthritis/collagen vascular diseases	3.1	2.2	2.9	2.7		0.050	0.007
	Coagulopathy	10.8	10.9	10.8	10.8		0.004	0.002
	Obesity	17.1	17.2	18.0	17.4		0.021	0.022
	Weight loss	6.7	6.8	6.9	6.8		0.002	0.007
	Fluid and electrolyte disorders	38.2	36.1	37.5	37.3		0.029	0.015
	Blood loss anemia	2.4	2.9	2.7	2.7		0.011	0.019
	Deficiency anemias	37.1	37.1	38.4	37.5		0.027	0.027
	Alcohol abuse	11.3	11.2	12.5	11.7		0.039	0.037
	Drug abuse	5.8	5.6	5.7	5.7		0.003	0.008
	Psychoses	9.5	9.1	9.8	9.5		0.023	0.010
	Depression	18.5	18.2	19.0	18.6		0.020	0.012

Abbreviations: HF = heart failure; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta blocker; combined therapy = ACEI or ARB and BB; CABG = coronary artery bypass grafting; AMI = acute myocardial infarction; eGFR = estimated glomerular filtration rate according to the CKD-EPI equation; VAMC = VA Medical Center; SD= standard deviation

[a] Absolute standardized difference (percentile) in covariate means and proportions after matching for ACEI/ARB versus Combined, BB versus Combined

[b] Race values do not add up to 100% due to unknown race (<1%)
[c] Comorbid conditions include a total of 29 Elixhauser comorbid conditions and cardiac arrhythmias
[d] Potential contraindications to ACEIs include: pregnancy, renal failure, renal artery stenosis, angioedema, hypotension, systolic blood pressure < 85mmHg, serum potassium > 5.5 mEq/L, or creatinine clearance < 30 ml/min.
[e] Potential contraindications to BBs include: bradycardia, advanced atrioventricular block without a pacemaker, hypotension, asthma, broncheostasis, chronic obstructive pulmonary disease, pulse < 60 bpm, systolic blood pressure < 85 mmHg, or concomitant use of chronic respiratory medications at the time of index hospitalization
[f] Use of non-VA services = at least one Medicare outpatient visit in the year following the patient's index date

Table 1-3. Proportional Hazard Regression Models for All-Cause Mortality and Heart Failure Rehospitalization According to Therapy at Discharge from Heart Failure Hospitalization

	No. of events (%)				**BB vs. Combined [a]**	**ACEI/ARB vs. Combined [a]**	**BB vs. ACEI/ARB [b]**
	BB	**ACEI/ARB**	**Combined**		HR (97.5% CI)	HR (97.5% CI)	HR (97.5% CI)
All-cause mortality							
30 days	87 (5.2)	54 (3.2)	54 (3.2)		1.67 (1.13, 2.48)	1.00 (0.65, 1.55)	1.62 (1.10, 2.40)
6 months	321 (19.3)	317 (19.0)	266 (16.0)		1.28 (1.05, 1.55)	1.20 (0.99, 1.45)	1.08 (0.89, 1.30)
Hospitalization for heart failure							
30 days	330 (20.2)	295 (17.9)	318 (19.3)		1.07 (0.89, 1.30)	0.91 (0.75, 1.10)	1.19 (0.98, 1.44)
6 months	677 (43.0)	687 (43.3)	645 (40.5)		1.14 (0.99, 1.31)	1.04 (0.90, 1.20)	1.09 (0.95, 1.26)

Abbreviations: HR = hazard ratio; CI = confidence interval; BB = B-blocker; ACEI=angiotensin-converting-enzyme inhibitor; ARB=angiotensin receptor blocker

[a] Combined therapy with ACEI or ARB and BB used as reference category

[b] ACEI/ARB used as reference category

Table 1-4. Proportional Hazard Regression Models for All-Cause Mortality According to Treatment at Discharge after Censoring Patients Rehospitalized for Heart Failure

	BB vs. Combined [a]	**ACEI/ARB vs. Combined [a]**	**BB vs. ACEI/ARB [b]**
	HR (97.5% CI)	HR (97.5% CI)	HR (97.5% CI)
All-cause mortality			
30 days	1.74 (1.08, 2.80)	1.15 (0.68, 1.94)	1.56 (0.997, 2.44)
6 months	1.17 (0.88, 1.56)	1.04 (0.78, 1.40)	1.35 (1.01, 1.79)

Abbreviations: HR = hazard ratio; CI = confidence interval; BB = B-blocker; ACEI=angiotensin-converting-enzyme inhibitor; ARB=angiotensin receptor blocker

[a] Combined therapy with ACEI or ARB and BB used as reference category

[b] ACEI/ARB used as reference category

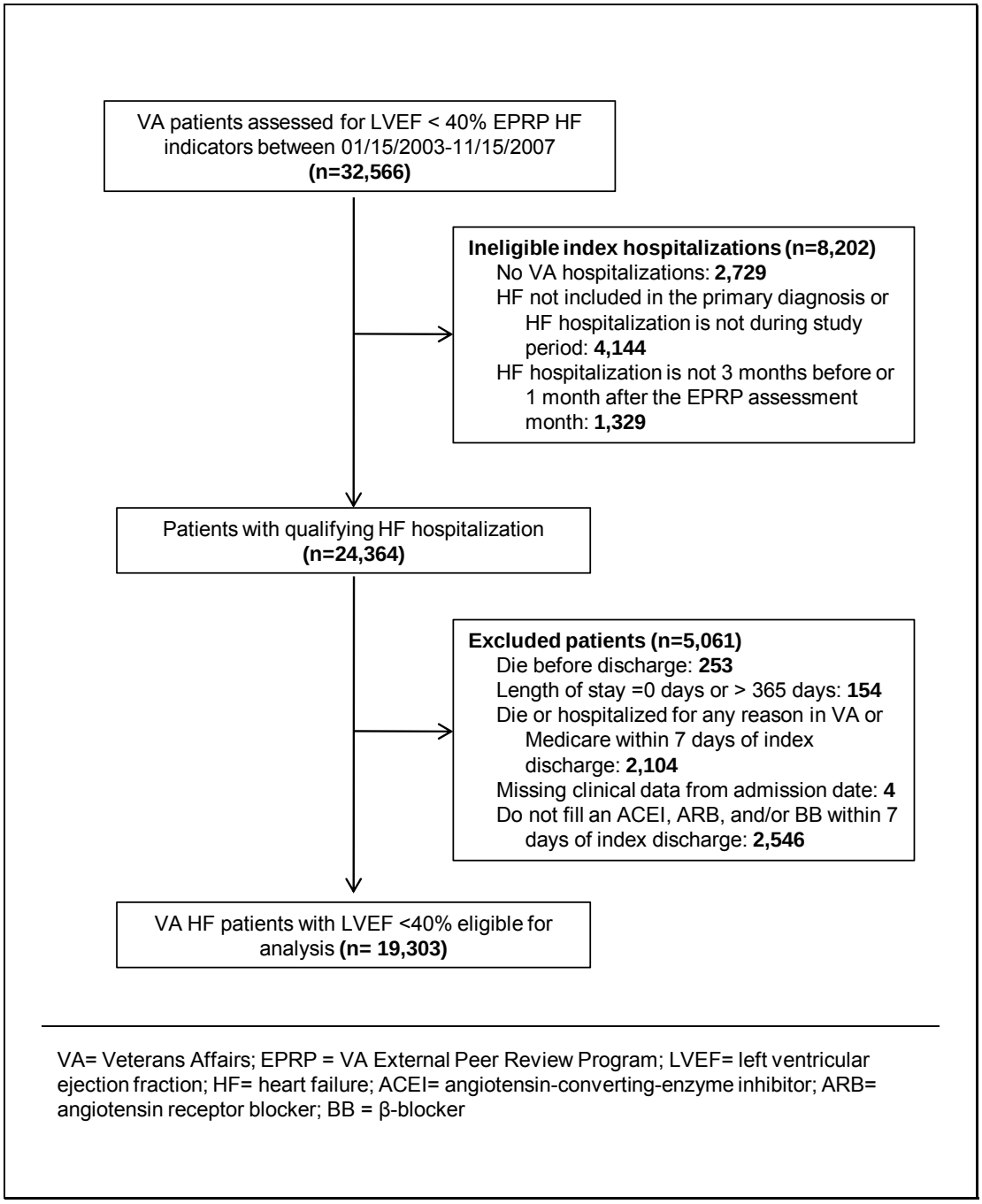

Figure 1-1. Selection of Study Cohort

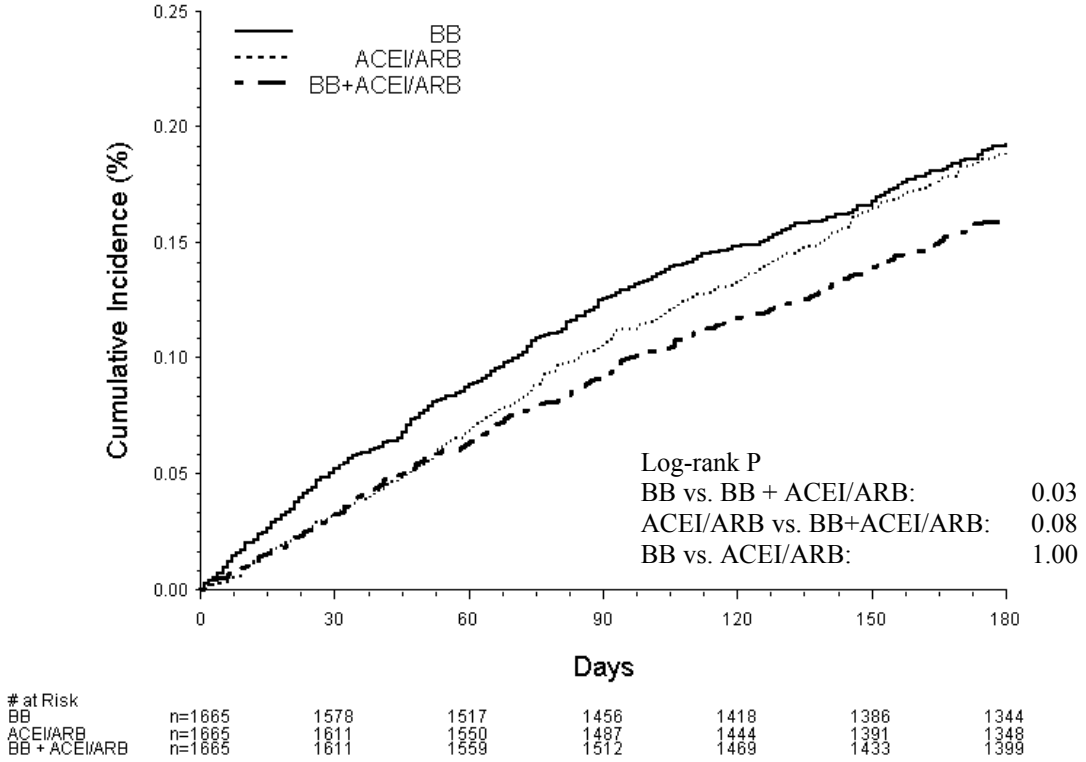

Figure 1-2. Cumulative Incidence of All-cause Mortality According to Therapy Received at Hospital Discharge

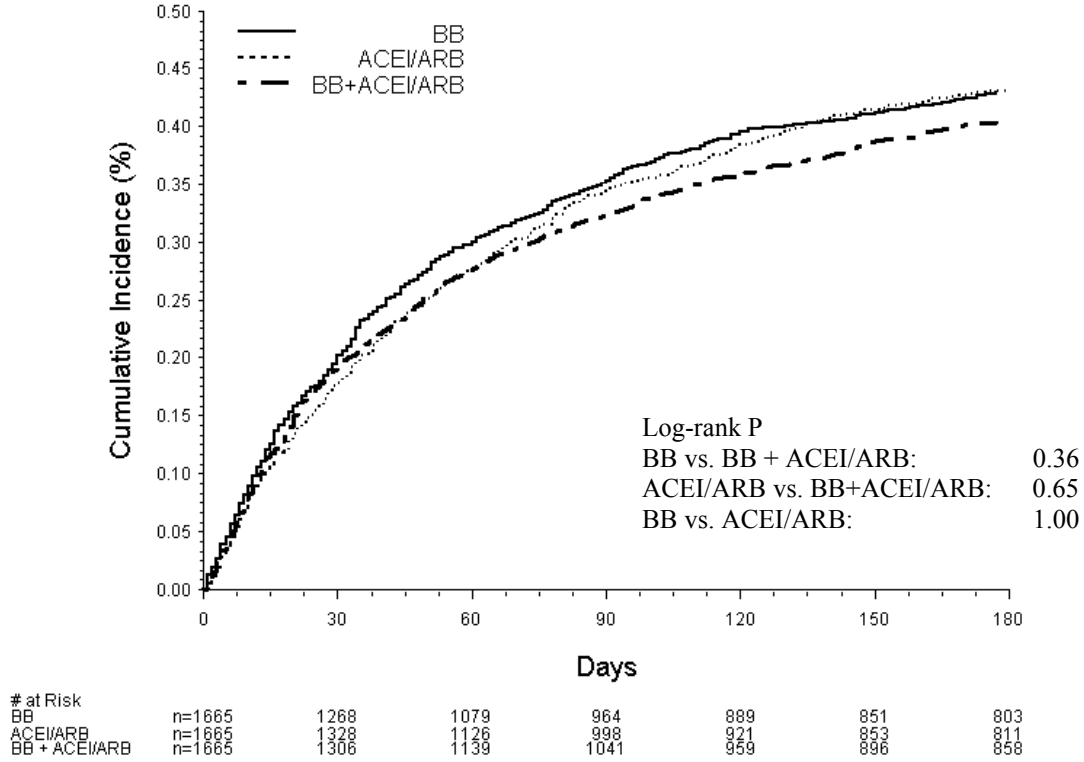

Figure 1-3. Cumulative Incidence of Rehospitalization for Heart Failure According to Therapy Received at Hospital Discharge

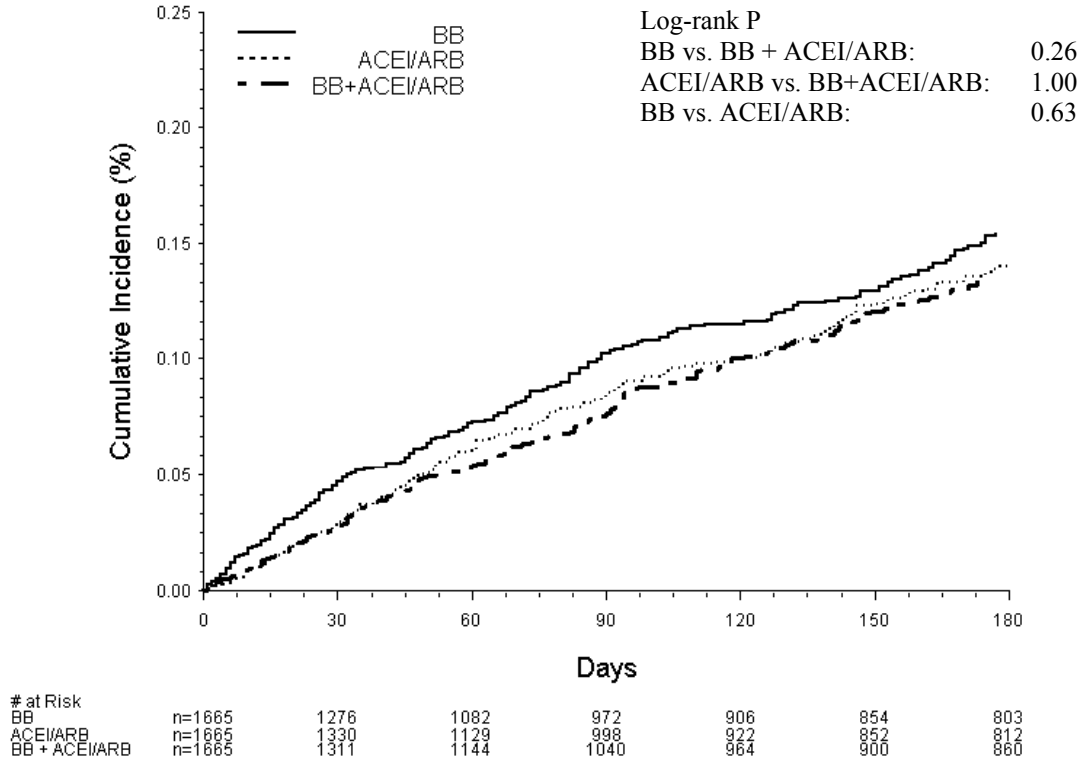

Figure 1-4. Cumulative Incidence of All-Cause Mortality According to Treatment at Discharge after Censoring Patients Rehospitalized for Heart Failure

CHAPTER 2 :
RENIN-ANGIOTENSIN SYSTEM INHIBITOR USE AT HEART FAILURE DISCHARGE IMPROVES CLINICAL OUTCOMES IN PATIENTS WITH RENAL DYSFUNCTION

Abstract

Context: Renin-angiotensin inhibitors are often used to slow the progression of kidney disease. However, limited and conflicting evidence about the effectiveness of angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) in patients with both chronic kidney disease and heart failure often precludes the use of these beneficial heart failure therapies in these patients.

Objective: To investigate the association between ACEI/ARB therapy at discharge and clinical outcomes among heart failure patients with reduced ejection fraction and renal dysfunction.

Design, Setting, and Participants: Retrospective cohort study among 10,628 veterans hospitalized for heart failure with left ventricular ejection fraction <40% at Veterans Affairs Medical Centers nationwide between 2003 and 2007 with at least one outpatient serum creatinine measurement before admission and baseline estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2. Renal function was estimated using the CKD-EPI equation. Patients were propensity-matched within categories of eGFR based on severity of kidney disease (15-29, 30-44, 45-59 ml/min/1.73m^2).

Main Outcome Measures: One year all-cause mortality, rehospitalization for heart failure, and composite of doubling of baseline serum creatinine or end-stage-renal disease to reflect worsening renal function.

Results: Among 4,224 matched patients, the receipt of an ACEI or ARB at hospital discharge among patients with both heart failure and renal dysfunction was associated with a significant reduction in heart failure rehospitalization within one year (HR: 0.80; 95% CI: 0.72, 0.89; log-rank P <0.0001). We observed nonsignificant reductions in one-

year all-cause mortality (HR 0.91, 95% CI: 0.82, 1.02; log-rank P= 0.05) and worsening renal function (HR: 0.90, 95% CI: 0.75, 1.09; log-rank P= 0.22). The association between the receipt of ACEI or ARB at discharge and outcomes was consistent across categories of eGFR. Patients with eGFR 30 to 44 ml/min/1.73m^2, in our study who received an ACEI or ARB at discharge experienced a17% reduction in the risk of all-cause mortality (HR: 0.83; 95% CI: 0.70, 0.98), and did not find evidence of worsening renal function among patients with eGFR 15 to 29 ml/min/1.73m^2 who received an ACEI or ARB at discharge.

Conclusion: Among veterans with chronic kidney disease hospitalized for heart failure with reduced ejection fraction, receipt of an ACEI or ARB at hospital discharge was associated with lower risk of heart failure rehospitalization. Discharge ACEI/ARB therapy was not associated with worsening renal function among patients with HF with LVSD and renal dysfunction in our study.

Introduction

Chronic kidney disease (CKD) occurs in over half of patients hospitalized with heart failure (HF) and is associated with a higher mortality risk compared with HF patients without CKD.[48-52] The coexistence of cardiac and renal dysfunction among these patients occurs as a result of systemic vasoconstriction by the renin-angiotensin system to counteract impaired glomerular function. Although numerous clinical trials have shown renin-angiotensin system inhibition with angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) reduce the risk of mortality, hospitalization, and worsening renal function among HF patients without kidney disease,

HF patients with kidney disease are less likely to receive an ACEI or ARB among their therapeutic regimen for HF.[9] The underuse of ACEIs/ARBs among patients with both conditions can be attributed to increases in serum creatinine observed in clinical trials of HF patients with impaired kidney function after initiating therapy with ACEIs and ARBs.[53, 54] Additionally, because patients with a serum creatinine ≥2.5 mg/dL have been systematically excluded from HF clinical trials of ACEIs and ARBs, there is limited evidence about the safety and efficacy of ACEIs and ARBs in HF patients with reduced left ventricular ejection fraction (LVEF) and moderate or severe kidney dysfunction.[8]

Available information about the association between the use of ACEIs and ARBs and outcomes among HF patients with chronic kidney disease is equivocal. While some studies reported significant reductions in the risk of all-cause mortality and HF hospitalization among HF patients with renal dysfunction treated with ACEIs or ARBs, a mortality benefit was observed only among HF patients with GFR >60 ml/min in other studies.[55-62] Two recent studies, however, suggest a mortality benefit among HF patients with kidney disease treated with ACEIs and ARBs.[56, 63] We therefore studied a nationwide cohort of patients hospitalized in the Veterans Affairs (VA) Health Care System for HF with LVEF <40% with renal dysfunction. We examined the relationship between the receipt of ACEI or ARB therapy at discharge from a HF hospitalization and clinical outcomes, including all-cause mortality and rehospitalization for HF among patients with chronic kidney disease. Additionally, because the renoprotective effects of renin-angiotensin system inhibition have been demonstrated in CKD patients without HF, we investigated whether ACEI or ARB therapy at discharge was related to renal outcomes among patients with HF and comorbid renal dysfunction.

Methods

Study Design

Veterans age 18 years or older who were hospitalized for HF with LVEF <40% at a VA medical center between January 15, 2003 and November 15, 2007 were identified using data from the VA External Peer Review Program (EPRP). The VA's Office of Quality and Performance contracts trained medical reviewers to abstract charts from a random nationwide sample of veterans in the EPRP to evaluate the quality of care delivered by VA facilities according to evidence-based performance measures. The EPRP sampling frame includes all VA beneficiaries with at least two years of continuous enrollment and who had at least one VA outpatient visit or hospitalization in the year prior to the assessment period. [16, 17]

Participants

Patients were identified using three EPRP performance measures for ACEI/ARB use among HF patients with LVEF <40%. To be eligible, patients must have a principal discharge diagnosis of HF and chart documentation of LVEF <40% or a narrative description of moderate or severe left systolic dysfunction. Exclusion criteria for these measures included allergy to both an ACEI and ARB, moderate or severe renal artery stenosis, participation in a clinical trial, and transfer to another hospital or hospice care.[18] For patients with multiple EPRP assessments (7,203/32,566; 22%), we used the earliest inpatient assessment during the study period. Because the EPRP data does not

specify the hospitalization assessed, we selected the closest VA HF hospitalization up to three months before or one month after their EPRP assessment date. We defined hospitalization for HF using *International Classification of Diseases, Ninth Revision* [*ICD-9-CM*] codes in the patient's primary diagnosis: 428.0 (congestive HF, unspecified), 428.1 (left HF); 428.2 (systolic HF) which is unspecified (428.20), acute (428.21), chronic (428.22), or acute or chronic (428.23); 428.3 (diastolic HF) which is unspecified (428.30), acute (428.31), chronic (428.32), or acute or chronic (428.33); 428.4 (combined systolic and diastolic HF), which is unspecified (428.40), acute (428.41), chronic (428.42), or acute or chronic (428.43); 428.9 (HF, unspecified); 398.91 (rheumatic HF); 402.01, 402.11, or 402.91 (hypertensive heart disease with HF); and 404.01, 404.03, 404.11, 404.13, 404.91, or 404.93 (hypertensive heart disease and chronic kidney disease with HF). Same-day readmissions for HF were treated as a single hospital stay. To be eligible for inclusion in this study, patients were also required to have at least one outpatient serum creatinine measurement up to six months before admission.

A total of 21,853 patients were identified using the EPRP dataset who had an eligible VA HF hospitalization and at least one outpatient serum creatinine measurement up to six months before admission. We then restricted our sample to 12,618 patients with chronic kidney disease, defined by a baseline estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2. Patients with evidence of renal failure before their index admission (baseline eGFR <15 mL/min/1.73m^2, kidney transplant, or on dialysis) were excluded (n=646). Additional exclusion criteria included: death before discharge (n=163), a length of stay greater than one year or less than one day (n=70), and the occurrence of any study

outcome within 7 days of discharge (n=1,181). Our final sample included 10,628 patients hospitalized for HF. (Figure 2-1)

Data Sources

Information about inpatient and outpatient visits was obtained from the VA National Patient Care Database. Laboratory results and medication information were obtained from VA Decision Support System records. [19, 20] To account for use of Medicare services during the study period, we used data from the VA/CMS Data for Research project.[21] We ascertained a patient's vital status by combining the VA Beneficiary Identification and Record Locator Subsystem dataset with VA/CMS data linked to Medicare's Enrollment Database.

Assessment of Kidney Function

The mean of all outpatient serum creatinine values obtained up to six months before the patient's index HF hospitalization was used to estimate each patient's baseline glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[64] We then categorized baseline eGFR corresponding to three clinical stages of CKD: 45 to 59 mL/min/1.73m^2 (mild/moderate; Stage IIIa), 30 to 44 mL/min/1.73m^2 (moderate/severe; Stage IIIb), and 15 to 29 mL/min/1.73m^2 (severe; Stage IV).[65]

Exposure

We defined exposure to an ACEI and/or ARB by the receipt of these medications on the final day of a patient's index HF hospitalization or by an outpatient fill within seven days of discharge. [22, 23] The index date of observation for all patients is seven days after discharge from the patient's index HF hospitalization to allow time for the majority of patients to fill discharge medications on an outpatient basis.

Outcomes

The primary outcome was one-year all-cause mortality. Secondary outcomes included rehospitalization for HF identified using both the VA and Medicare datasets, and a composite outcome of end-stage renal disease, defined as initiation of dialysis or renal transplantation, and doubling of the baseline value of serum creatinine, whichever occurred first. All outcomes were assessed within one year of the patient's index date. Patients who died were censored in analyses of secondary outcomes. We defined dialysis by the presence of any ICD-9-CM codes for end-stage kidney disease requiring dialysis (585.6), dialysis (V45.1), hemodialysis (V56.0, V56.1, V56.31, 39.95), and peritoneal dialysis (V56.2, V56.32, V56.8, 54.98); Current Procedural Terminology (CPT-4) codes: 90921, 90925, 90935, 90937, 90945, 90947, 90999, 90989, and 90993; or if an admission was assigned to diagnosis related group (DRG) code 317. Renal transplant was defined by the presence of ICD-9-CM: V42.0; CPT-4: 50360 or 50365; or DRG: 302 or 512. Complete information on all outcomes was available through December 31, 2008.

Patient Characteristics/Covariates

Sociodemographic characteristics included the presence of any service-connected disability, medication copayments using the VA means test indicator, and marital status. We used the most frequent value of self-identified patient race and categorized patients as white, black (including Non-Hispanic Black or African American), or other (including Hispanic or Latino, American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander).[24] For patients whose race could not be determined from the VA datasets (3%), we substituted race, when available, from the VA/CMS dataset. We assigned the VA Medical Center that provided treatment to U.S. Census Regions. We also examined length of stay, and long-term care admissions up to 6 months before admission and during follow-up. We used VA/CMS Medicare outpatient claims to identify whether patients sought non-VA care during the study period.

We obtained laboratory, vital sign information, and demographic characteristics reported at admission. The value of serum creatinine closest to admission was substituted for 312 patients (2.9%) in the final sample missing this measurement. Body mass index (BMI) was calculated from the patient's weight up to six months before admission and height recorded at any time. We examined two-year history of HF hospitalization, coronary artery disease, acute myocardial infarction (AMI), angina, percutaneous coronary intervention (PCI), coronary bypass grafting (CABG), atrial fibrillation, and the presence of a pacemaker or implantable defibrillator. We also examined concomitant use of other HF therapies at discharge. Prior ACEI or ARB use was defined as the receipt of these medications in the 90 days before admission. We assessed patients for the presence of potential contraindications to treatment with ACEIs or ARBs, which included

pregnancy within one year of the index admission, co-morbid renal artery stenosis, angioedema, hypotension, and systolic blood pressure < 85mmHg or serum potassium > 5.5 mEq/L at admission.[25]

Comorbid conditions were identified using VA and Medicare inpatient and outpatient claims from the two years prior to index hospitalization. Elixhauser Comorbidity Index software available on the Agency for Healthcare Research and Quality (AHRQ) website was used to identify 28 conditions (excluding HF and renal failure) and modified to include cardiac arrhythmias.[26] A patient's sum of comorbidities (their total of the 28 conditions) was included as an additional covariate.

Statistical Analyses

Missing values for potential confounders including hematocrit (6.4%), BMI (4.0%), and sodium, potassium, systolic blood pressure, diastolic blood pressure, and pulse, which were missing in 1-2% of the overall sample, were imputed using mean values from 10 imputed datasets. Missing values of hematocrit were estimated with hemoglobin values (hemoglobin x 3) when available.[27] Baseline characteristics according to receipt of ACEI/ARB at discharge and baseline eGFR category before matching were compared using chi-square tests for categorical variables and t-tests for continuous variables.

Because patients were not randomly assigned to receive ACEI/ARB therapy, we performed propensity-score matching to account for potential confounding and selection bias. The probability of receiving an ACEI or ARB at discharge was modeled using three nonparsimonious multivariable logistic regression models including all Table 2-1

covariates according to baseline CKD stage. The *c* statistics for the propensity score models were 0.78 (eGFR 45 to 59 mL/min/1.73m^2), 0.79 (eGFR 30 to 44 mL/min/1.73m^2), and 0.78 (eGFR 15 to 29 mL/min/1.73m^2), which indicated strong ability to discriminate between ACEI/ARB recipients and non-recipients within each eGFR category. Patients were then 1:1 matched within category according to the modeled propensity score using an iterative Greedy 5-to-1 digit matching algorithm to select the closest match.[66] To evaluate the effectiveness of matching, the distribution of patient characteristics before and after matching was compared using absolute standardized differences, expressed as percentages, in covariate means and proportions by eGFR category. A standardized difference < 0.10 suggests similar distribution among groups.[38, 39]

We estimated event-free survival probabilities for study outcomes and compared survival according to the receipt ACEI/ARB therapy at discharge of using the Kaplan–Meier method. Differences between survival curves were compared using the log-rank test. Cox proportional hazards regression for the combined propensity-matched samples was used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the association between ACEI/ARB therapy at discharge and study outcomes among patients with CKD and HF. The appropriateness of the proportional hazards assumption was assessed for each model using tests of Martingale residuals. As a sensitivity analysis, we ascertained potential heterogeneity of the association between ACEI/ARB therapy and outcomes in different stages of kidney disease by repeating the Cox regression for each outcome according to eGFR category.

All analyses were performed with SAS 9.2 (SAS Institute, Cary, NC). The Providence VA Medical Center institutional review board approved the study protocol.

Results

Baseline Characteristics

Chronic kidney disease is common among patients with HF with LVSD and occurred among 58% of patients with baseline serum creatinine values in our original cohort (12,618 / 21,853). A total of 10,628 patients hospitalized for HF with LVEF <40% were included in our study population. The mean baseline eGFR in the unmatched sample was 42.6±11.1 mL/min/1.73m^2 (Median: 44.0 mL/min/1.73m^2; IQR: 34.4 – 51.9 mL/min/1.73m^2) and mean baseline serum creatinine was 1.7±0.5 mg/dL. (Figure 2-2) In the overall unmatched cohort, 3,404 (32.0%) patients died in one year, and all-cause mortality was highest among patients with eGFR <15-29 mL/min/1.73m^2 (42.4%). Rehospitalization for HF occurred in 5,310 (50.0%) patients and was more frequent among patients in the lower eGFR categories. The composite outcome of ESRD and doubling of serum creatinine occurred in 19% of patients with eGFR <15-29 mL/min/1.73m^2, compared with 8% of patients in each of the other eGFR categories. ACEI/ARB use at hospital discharge was less common among patients with lower eGFR. Only 57% of patients with eGFR <15-29 mL/min/1.73m^2 received an ACEI or ARB compared with 80% of patients with eGFR 45-59 mL/min/1.73m^2. (Table 2-1)

Propensity-Matched Population

We matched 65% (eGFR <15-29 mL/min/1.73m^2), 78% (30 to 44 mL/min/1.73m^2) and 78% (eGFR 45 to 59 mL/min/1.73m^2) of patients to ACEI/ARB recipients within the same baseline eGFR category for our primary analyses. This approach yielded a 75% (2,112/2,826) overall match rate for our propensity-matched sample. Predictors of the receipt of ACEI/ARB at discharge in each propensity score model included mean blood pressure, previous ACEI or ARB therapy, and concurrent receipt of aspirin, β-blockers, digoxin, or diuretics at discharge. Patients receiving hydralazine at discharge were significantly less likely to receive an ACEI or ARB at discharge within each model (data not shown). After matching, standardized differences were <10% for all measured covariates within each eGFR category and suggest that matching improved the balance in distribution of covariates between ACEI/ARB recipients and non-recipients. (Table 2-2)

Baseline characteristics of the propensity-matched patients, by eGFR category, are shown in Table 2-2. Among 4,224 matched patients, the mean age was 73.3 ± 10.6 years, 74% were white, and patients were predominantly male. A history of CAD was present among 84%, and common comorbid conditions included hypertension (91%), COPD (48%), uncomplicated (26%) and complicated (30%) diabetes mellitus. Compared to patients in higher eGFR categories, patients with eGFR 15-29 mL/min/1.73m^2 had higher mean blood urea nitrogen and lower mean hematocrit values, a higher mean number of comorbid conditions, particularly anemia and fluid and electrolyte disorders, a longer stay during their index HF hospitalization, and sought outpatient non-VA care more often. Although the proportion of patients with diabetes mellitus was similar across categories of eGFR, patients with lower eGFR were more likely to have complications

related to diabetes. Lower eGFR was also associated with more frequent use of aspirin, β-blockers, calcium channel blockers, loop diuretics, hydralazine, and nitrates. In contrast, patients with eGFR 45-59 mL/min/1.73m^2 were more likely than patients with lower eGFR to receive digoxin and potassium-sparing diuretics, while patients with eGFR 30-44 mL/min/1.73m^2 were the most likely to have comorbid COPD.

Outcomes According to eGFR and ACEI/ARB Therapy

All cause mortality

All-cause mortality within one year was 36.4% in the propensity-matched sample and the proportion of patients with eGFR 15 to 29 mL/min/1.73m^2 who died was nearly double that of patients with eGFR 45-59 mL/min/1.73m^2 (44.8% vs. 27.8%). (Table 2-3) The Kaplan-Meier plot showed a borderline survival difference (log-rank P=0.05) according to ACEI or ARB therapy at discharge, and our Cox model showed a nonsignificant reduction in all-cause mortality among ACEI/ARB recipients within one year compared with patients who did not receive ACEI/ARB therapy (HR 0.91; 95% CI: 0.82, 1.02). (Figure 2-3)

Heart failure rehospitalization

Over half of patients in the propensity-matched sample were rehospitalized for HF within one year (2,168 patients; 51%). The rate of rehospitalization decreased from lower to higher eGFR categories. (Table 2-3) Compared with patients who did not receive ACEI/ARB therapy at discharge, ACEI/ARB therapy at discharge was associated

with a 20% reduction in the risk of one-year rehospitalization for HF (HR: 0.80; 95% CI: 0.72, 0.89; log-rank P<0.0001). (Figure 2-4)

ESRD or doubling of serum creatinine

During follow-up, 237 (6%) patients in the propensity-matched sample developed ESRD, and 457 (10.8%) patients had the composite outcome of ESRD or doubling of serum creatinine. The rate of the composite outcome doubled among patients in the eGFR 15-29 mL/min/1.73m^2 category when compared with patients in both eGFR 30-44 and 45-59 mL/min/1.73m^2 categories (20% vs. 8% for both comparisons). The Kaplan-Meier survival curves are shown in Figure 2-5 but did not diff according to the receipt of ACEI/ARB therapy (log-rank P=0.22). Our Cox regression estimated a nonsignificant reduction in the hazard of the composite renal outcome among ACEI/ARB therapy recipients (HR: 0.90; 95% CI: 0.75, 1.09). A violation of the proportional hazards assumption was detected for our composite renal outcome (p=0.02) and inspection of the negative log-log plot for this model indicating crossing hazards at approximately 70 days. However, the addition of an interaction between treatment and survival time dichotomized at the point of convergence to the model was not statistically-significant (P=0.98).

Sensitivity Analysis

After repeating our Cox regression models individually for each eGFR category, we observed that the association between all-cause mortality and receipt of ACEI/ARB

therapy did not vary significantly between eGFR categories. (Table 2-4) There were non-significant reductions in all-cause mortality for patients who received an ACEI or ARB at discharge for the eGFR 15-29 and 45-59 mL/min/1.73m^2 categories, and a 17% reduction in all-cause mortality among patients with eGFR 30-44 mL/min/1.73m^2. The hazard of HF rehospitalization was significantly reduced among patients in each eGFR category. For the composite outcome of ESRD or doubling of serum creatinine, patients with eGFR 45 to 59 mL/min/1.73m^2 had a nonsiginficant reduction in risk (HR: 0.73; 95% CI: 0.51, 1.04). However, even among patients with eGFR 15 to 29 mL/min/1.73m^2 category, who were at greatest risk for this outcome, ACEI/ARB therapy was not associated with ESRD or doubling of serum creatinine (HR: 1.05; 95% CI: 0.78, 1.42).

Discussion

In this propensity-matched study of veterans hospitalized for HF with LVEF <40% and comorbid renal dysfunction, we observed an overall 14% to 20% reduction in the risk of HF rehospitalization among patients with CKD who received an ACEI or ARB at HF hospital discharge. This finding is particularly relevant when considering that over half of patients hospitalized for HF with LVEF <40% in our original sample for whom we could assess baseline eGFR had an eGFR <60 mL/min/1.73m^2, consistent with previous estimates of kidney disease in an acute decompensated HF population.[48] We did not find evidence of an association between ACEI or ARB therapy at discharge and all-cause mortality. Additionally, ACEI or ARB therapy at discharge among patients with HF with LVSD and renal dysfunction was not associated with an increased risk of the combined ESRD or doubling of baseline serum creatinine outcome

We observed that the association between receipt of ACEI/ARB therapy at discharge and study outcomes did not vary significantly in either magnitude or direction according to severity of kidney disease, suggesting that ACEI/ARB therapy at discharge may be beneficial among patients with any level of underlying renal dysfunction. Patients with the lowest baseline eGFR in our study, however, received ACEI/ARB 25% less often compared with patients with higher eGFR.

In a recent subgroup analysis of patients with CKD and LVEF ≤35% in the Studies of Left Ventricular Dysfunction (SOLVD)-Treatment trial, patients with CKD with a mean eGFR 49±8 mL/min/1.73m^2 treated with enalapril experienced a non-significant reduction in all-cause mortality and significant reduction in the risk of rehospitalization for cardiovascular disease.[63] While our findings are consistent with this study, patients in our study had lower mean renal function, acute decompensated HF, and higher rates of β-blocker use. We also report the results for shorter-term outcomes (one year versus a median follow-up of 35 months in the SOLVD study). Earlier observational studies and secondary analyses of clinical trial data also observed reductions in mortality among patients receiving an ACEI or ARB independent of renal function, consistent with our results.[58, 60-62]

Our findings are also in agreement with earlier observational studies which found ACEI or ARB therapy did not reduce the risk of mortality among patients with CKD.[55, 59] However, our study methodology differed by comparing patients with similar probabilities of receiving an ACEI or ARB on the basis of numerous characteristics. A recent propensity-matched study of 888 Medicare beneficiaries in Alabama with LVEF <45% hospitalized for HF found patients with CKD, as well as those with eGFR <45

mL/min/1.73^2, experienced lower risks of mortality when treated with an ACEI or ARB at discharge.[56] In contrast with the SOLVD analysis, as well as our study, the authors did not find a significant reduction in the risk of HF rehospitalization associated with ACEI/ARB therapy. Although renal function was similar in this study compared with ours (eGFR 37±13 vs. 43 ± 11 mL/min/1.73m^2, respectively), only 25% of patients in this study received β-blocker therapy, we evaluated a larger and nationally-representative population of HF patients, and our study examines more immediate (1 year vs. 8 year) outcomes. Whereas Ahmed *et al*. used admission serum creatinine to estimate renal function, we estimated a stronger surrogate of underlying renal dysfunction using outpatient serum creatinine before admission.[67]

Although treatment with ACEIs has been associated with worsening renal function in HF patients[68, 69], and protection from kidney disease progression among non-HF patients[70], we found a reduction in the hazard of our composite renal outcome with ACEI/ARB therapy at discharge. In the CONSENSUS study, increases in serum creatinine associated with initiation of enalapril therapy occurred during the first few weeks of treatment, and pre-treatment serum creatinine doubled among 11% of patients.[53] Although fewer patients in our study experienced doubling of serum creatinine during follow-up, the majority were treated with an ACEI or ARB before their index admission. Although we did not evaluate whether patients experienced a mild treatment-related decline in renal function, our findings agree with a recent study illustrating early, minor decreases in renal function associated with the initiation of ACEI therapy in patients with HF with reduced LVEF were not associated with an increase risk of adverse events.[68]

The strengths of this study include a large, nationally-representative, sample of veterans for which we had comprehensive information on clinical measures and outcomes in both the VA and Medicare. Whereas most randomized controlled trials of ACEIs/ARBs excluded patients with a serum creatinine above 2.5 mg/dL, propensity-matched patients in our lowest eGFR category had a mean serum creatinine of 2.7 mg/dL. The mean serum creatinine among patients with reduced LVEF studied in ACEI/ARB trials ranges from 1.2 mg/dL in SOLVD to 1.5 mg/dL in CONSENSUS, compared with 1.9 mg/dL in our study. Furthermore, because the VA Health Care System serves a sizable patient population, we had a large study sample of HF patients from which to derive a propensity-matched sample and high match rate.

Our study also has many limitations. Because we did not have access to electronic medical records identifying discharge medications and used administrative pharmacy data, we utilized a proxy definition of ACEI/ARB therapy at discharge that considered the possibility that patients might fill a prescription for discharge medications on an outpatient basis. As a result, we extended the index date of our study to a week post-discharge to allow time for patients to obtain the study medications. Although earlier studies assessing discharge medications using claims data found the majority of patients filled discharge medications during this timeframe[22], there remains the possibility of exposure misclassification in our study. We expect this bias to be random and result in the underestimation of the association between ACEI/ARB therapy and our study outcomes. Although we were able to identify non-VA hospitalizations using VA/CMS data, we could not fully capture non-VA utilization among VA patients without Medicare. Indeed, only 59% of patients with qualifying VA HF hospitalizations (14,397/ 24,364)

also had an inpatient or outpatient claim in the VA/CMS dataset and may have led us to underestimate HF rehospitalization and non-VA utilization. Our analyses were also limited by approximating renal function and outcomes using an estimated baseline renal function, as well as defining the outcome of doubling serum creatinine based on a single outpatient measurement during follow up. Although we chose to use the mean of outpatient values prior to admission, we cannot rule out the possibility of misclassification of baseline eGFR.[67] Another limitation of our study is the use of observational data. While we attempted to address the potential of confounding through our propensity-matching method, our results are not free from residual confounding by unmeasured covariates. Finally, the results of our study may not be generalizable to women, patients with diastolic HF, and patients with an eGFR <15 mL/min/1.73m^2.

Conclusion

In summary, we found that among a large propensity-matched cohort of veterans hospitalized for HF with LVEF <40%, ACEI/ARB therapy at hospital discharge was associated with a significant reduction in the risk of rehospitalization for HF, but was not associated with an increased risk of ESRD or doubling of serum creatinine among patients with comorbid CKD. Paradoxically, our study suggests that patients less likely to receive ACEI/ARB therapy due to renal dysfunction on the basis of perceived adverse clinical outcomes are also more likely to benefit from ACEI/ARB therapy. Our findings provide further evidence in support the use of these therapies among HF patients with CKD.

Tables and Figures

Table 2-1. Baseline Characteristics of Patients Hospitalized for Heart Failure with LVEF <40%, by Baseline eGFR Category and Receipt of ACEI or ARB at Discharge (n=10,628)

	Baseline Estimated Glomerular Filtration Rate (ml/min per 1.73m2)												
	15-29			**30-44**			**45-59**			**Overall**			**Total**
Baseline Characteristic	No ACEI/ ARB n=725	ACEI/ ARB n=949	P-value	No ACEI/ ARB n=1,079	ACEI/ ARB n=2,895	P-value	No ACEI/ ARB n=1,022	ACEI/ ARB n=3,958	P-value	No ACEI/ ARB n=2,826	ACEI/ ARB n=7,802	P-value	n=10,628
Age at index date, mean (SD), years	73.4 (10.5)	74.2 (10.7)	0.139	74.9 (9.9)	73.9 (10.2)	0.006	71.2 (10.7)	71.1 (10.9)	0.706	73.2 (10.5)	72.5 (10.7)	0.003	72.7 (10.6)
Female sex, %	0.4	0.5	0.740	0.9	0.6	0.247	1.4	0.8	0.094	1.0	0.7	0.168	0.8
Race, %a			0.762			0.505			0.415			0.074	
White	73.4	74.3		76.4	74.9		72.8	71.2		74.3	73.0		73.3
Black	17.9	18.4		16.4	18.1		19.1	21.0		17.8	19.6		19.1
Other	8.4	7.1		7.0	6.7		7.8	7.3		7.7	7.0		7.2
Married, %	51.7	48.2	0.218	52.3	48.7	0.109	49.3	46.8	0.292	51.1	47.7	0.008	48.6
Any service-connected disability, %	31.9	30.0	0.422	30.7	30.7	0.999	28.4	29.3	0.548	30.2	29.9	0.817	30.0
Required copayment, %	10.2	11.4	0.445	11.0	10.5	0.631	10.5	10.6	0.933	10.6	10.6	0.973	10.6
Previous ACEI or ARB therapy, %	42.2	61.9	<.0001	49.2	61.1	<.0001	54.5	58.1	0.040	49.3	59.7	<.0001	56.9
Contraindications to ACEI therapy, %b	25.8	22.8	0.151	25.1	20.0	0.000	21.0	17.2	0.004	23.8	18.9	<.0001	20.2
Laboratory values, mean (SD)													

Baseline serum creatinine, mg/dL	2.7 (0.5)	2.6 (0.5)	<.0001	1.8 (0.2)	1.8 (0.2)	0.102	1.4 (0.2)	1.4 (0.2)	0.813	1.9 (0.6)	1.7 (0.5)	<.0001	1.7 (0.5)
Baseline eGFR, mL/min/1.73m2	23.6 (4.1)	24.8 (3.8)	<.0001	37.6 (4.2)	38.3 (4.3)	<.0001	52.2 (4.2)	52.5 (4.3)	0.083	39.3 (11.9)	43.8 (10.6)	<.0001	42.6 (11.1)
Admission serum creatinine, mg/dL	2.7 (0.8)	2.5 (0.7)	<.0001	1.8 (0.4)	1.7 (0.4)	<.0001	1.4 (0.3)	1.4 (0.3)	0.004	1.9 (0.7)	1.6 (0.5)	<.0001	1.7 (0.6)
Blood urea nitrogen, mg/dL	54.1 (23.9)	47.8 (20.7)	<.0001	36.6 (14.6)	34.4 (13.9)	<.0001	28.1 (11.6)	26.1 (10.1)	<.0001	38 (19.4)	31.8 (15)	<.0001	33.5 (16.5)
Hematocrit, %	33.5 (5.2)	34.4 (5.4)	0.001	35.9 (5.4)	36.4 (5.5)	0.013	37.3 (5.3)	38.2 (5.5)	<.0001	35.8 (5.5)	37.1 (5.7)	<.0001	36.7 (5.6)
Serum sodium, mEq/L	138 (4)	138.3 (3.9)	0.166	138.2 (3.8)	138.2 (3.8)	0.993	137.9 (3.7)	138.2 (3.7)	0.038	138.1 (3.8)	138.2 (3.8)	0.073	138.2 (3.8)
Serum potassium, mEq/L	4.2 (0.6)	4.1 (0.6)	0.596	4.1 (0.6)	4.0 (0.5)	0.053	4.0 (0.5)	4.0 (0.5)	0.030	4.1 (0.6)	4.0 (0.5)	<.0001	4.0 (0.5)
Systolic BP, mmHg	130.8 (25.9)	134.4 (26.6)	0.006	128.6 (23.6)	131.1 (23.9)	0.003	128 (23.1)	131.8 (23.6)	<.0001	128.9 (24.1)	131.9 (24.1)	<.0001	131.1 (24.1)
Diastolic BP, mmHg	72 (16.1)	74.8 (16.3)	0.001	72.3 (14.7)	74.1 (15.8)	0.001	73.9 (14.8)	76.2 (15.8)	<.0001	72.8 (15.1)	75.2 (15.9)	<.0001	74.6 (15.7)
Mean BP, mmHg	91.6 (17.7)	94.6 (18)	0.001	91 (15.8)	93.1 (16.7)	0.001	91.9 (15.7)	94.7 (16.7)	<.0001	91.5 (16.3)	94.1 (16.9)	<.0001	93.4 (16.8)
Pulse, bpm	79.1 (16.9)	79.5 (17.8)	0.670	80.1 (17.1)	79.5 (17.3)	0.284	81.8 (18.4)	82.6 (18.1)	0.219	80.5 (17.6)	81.1 (17.9)	0.136	80.9 (17.8)
Body mass index, kg/m2	28.9 (6.3)	28.3 (6)	0.061	28.7 (6.1)	28.8 (6.1)	0.539	29.1 (7.2)	29.5 (6.6)	0.158	28.9 (6.6)	29.1 (6.3)	0.189	29 (6.4)
Discharge medication use, %													
Anti-arrhythmic drugs	7.5	9.5	0.141	6.9	7.2	0.694	5.3	6.6	0.132	6.4	7.2	0.195	7.0
Anticoagulants	37.4	45.9	0.000	33.5	50.2	<.0001	31.6	50.4	<.0001	33.8	49.8	<.0001	45.5
Aspirin	45.8	55.7	<.0001	33.7	57.9	<.0001	32.6	59.9	<.0001	36.4	58.7	<.0001	52.7
β-blockers	63.6	79.5	<.0001	51.4	78.5	<.0001	48.7	80.3	<.0001	53.6	79.5	<.0001	72.6
Calcium channel blockers	16.1	18.0	0.312	9.2	11.7	0.023	7.1	10.9	0.000	10.2	12.1	0.010	11.6
Digoxin	18.6	28.8	<.0001	20.2	36.4	<.0001	22.7	39.8	<.0001	20.7	37.2	<.0001	32.8
Loop diuretics	73.0	89.0	<.0001	65.3	88.9	<.0001	62.2	88.3	<.0001	66.1	88.6	<.0001	82.6

Potassium-sparing diuretics	10.5	18.7	<.0001	12.9	25.8	<.0001	16.8	30.4	<.0001	13.7	27.3	<.0001	23.7
Other diuretics	9.1	11.7	0.087	6.9	8.7	0.055	6.7	6.6	0.923	7.4	8.0	0.280	7.8
Hydralazine	34.6	18.4	<.0001	15.7	9.7	<.0001	8.7	7.0	0.058	18.0	9.4	<.0001	11.7
Nitrates	48.4	45.0	0.165	32.7	37.4	0.007	24.7	35.1	<.0001	33.8	37.1	0.002	36.3
History of cardiovascular disease, %													
Previous heart failure hospitalization	36.0	35.7	0.906	30.9	30.7	0.909	27.4	22.5	0.001	30.9	27.2	0.000	28.2
Coronary artery disease	87.9	85.6	0.172	86.0	85.4	0.642	83.0	80.1	0.041	85.4	82.8	0.001	83.5
Acute myocardial infarction	51.5	49.0	0.321	49.0	48.4	0.737	49.5	43.2	0.000	49.8	45.9	0.000	46.9
Angina	26.9	22.8	0.051	25.5	23.9	0.290	26.5	23.3	0.030	26.2	23.4	0.003	24.2
Atrial fibrillation	41.1	43.4	0.343	47.5	46.8	0.717	45.7	42.1	0.039	45.2	44.0	0.282	44.3
Percutaneous intervention	6.8	6.2	0.655	6.4	6.2	0.775	7.5	5.8	0.041	6.9	6.0	0.085	6.2
Coronary artery bypass grafting	1.9	2.4	0.497	2.6	2.3	0.517	3.0	2.3	0.160	2.6	2.3	0.366	2.4
Pacemaker/defibrillator	28.1	30.4	0.325	31.5	27.7	0.017	28.8	23.0	0.000	29.7	25.6	<.0001	26.7
Fiscal year of index admission, mean (SD)	2005.3 (1.3)	2005.1 (1.4)	0.001	2005.3 (1.3)	2005.1 (1.4)	<.0001	2005.4 (1.4)	2005.2 (1.4)	0.001	2005.3 (1.3)	2005.2 (1.4)	<.0001	2005.2 (1.4)
VA Medical Center Census Region, %			0.050			0.080			0.012			<.0001	
Northeast	13.7	17.8		12.1	14.4		10.1	13.8		11.8	14.5		13.8
Midwest	26.9	22.2		25.3	21.9		25.2	21.9		25.7	21.9		22.9
South	40.8	43.0		43.5	44.2		44.5	44.5		43.2	44.2		43.9
West	17.1	15.3		17.4	18.2		18.1	17.8		17.6	17.6		17.6
Outside Census Regions	1.5	1.7		1.8	1.4		2.1	2.1		1.8	1.8		1.8
Length of index hospital stay, days, mean (SD)	6.7 (9.2)	6.6 (7.7)	0.695	6.3 (7.7)	5.5 (4.9)	0.000	5.7 (5.5)	5.3 (5.1)	0.057	6.2 (7.4)	5.5 (5.4)	<.0001	5.7 (6)

Admission to long-term care, %	17.2	15.1	0.230	15.9	14.3	0.195	13.2	11.9	0.235	15.3	13.2	0.005	13.7
Use of non-VA outpatient services, %	31.2	28.2	0.193	27.5	26.2	0.382	23.3	22.6	0.634	26.9	24.6	0.014	25.2
Number of comorbid conditions, mean (SD)c	5.9 (2.3)	5.6 (2.3)	0.030	5.6 (2.4)	5.3 (2.3)	0.000	5.2 (2.4)	4.8 (2.3)	<.0001	5.6 (2.4)	5.1 (2.3)	<.0001	5.2 (2.4)
Comorbid conditions, %c													
Cardiac arrhythmias	23.9	26.6	0.210	27.3	27.2	0.939	28.8	25.3	0.023	27.0	26.2	0.399	26.4
Valvular disease	31.5	30.1	0.564	32.8	31.4	0.385	29.1	28.7	0.796	31.1	29.8	0.209	30.2
Pulmonary circulation disorders	14.9	13.5	0.412	16.1	14.2	0.127	14.6	12.4	0.064	15.3	13.2	0.007	13.8
Peripheral vascular disease	36.8	35.0	0.436	32.0	29.9	0.210	26.2	23.6	0.075	31.1	27.3	0.000	28.3
Hypertension	93.7	94.0	0.775	91.8	92.8	0.337	88.1	89.1	0.366	90.9	91.0	0.890	91.0
Paralysis	5.1	4.5	0.587	4.7	3.9	0.268	4.2	4.3	0.902	4.6	4.2	0.319	4.3
Other neurological	6.5	7.1	0.642	6.3	6.2	0.922	7.1	6.9	0.783	6.7	6.7	0.982	6.7
Chronic pulmonary disease	47.2	45.6	0.530	50.3	47.4	0.104	49.7	43.8	0.001	49.3	45.4	0.000	46.4
Diabetes (uncomplicated)	19.6	21.9	0.245	25.4	26.2	0.614	30.2	29.2	0.510	25.7	27.2	0.115	26.8
Diabetes (complicated)	41.4	38.4	0.210	31.8	29.7	0.212	22.3	23.6	0.385	30.8	27.7	0.002	28.5
Hypothyroidism	16.0	16.1	0.946	17.6	16.0	0.222	14.0	10.8	0.005	15.9	13.4	0.001	14.1
Liver disease	3.7	4.2	0.612	4.5	4.6	0.907	4.8	4.6	0.737	4.4	4.5	0.802	4.5
Peptic ulcer disease	0.1	0.3	0.459	0.3	0.4	0.630	0.4	0.2	0.360	0.3	0.3	0.921	0.3
AIDS/HIV	0.4	0.2	0.451	0.1	0.3	0.222	0.4	0.2	0.360	0.3	0.3	0.812	0.3

Lymphoma	1.2	0.7	0.294	1.1	1.2	0.802	1.8	1.3	0.310	1.4	1.2	0.507	1.3
Metastatic cancer	0.3	1.0	0.092	1.4	1.0	0.298	1.4	1.3	0.787	1.1	1.1	0.893	1.1
Solid tumor without metastasis	12.0	13.0	0.556	15.8	12.7	0.013	11.9	11.6	0.728	13.4	12.2	0.082	12.5
Rheumatoid arthritis/collagen vascular diseases	1.8	3.4	0.048	2.8	2.8	0.930	2.8	2.8	0.885	2.6	2.9	0.389	2.8
Coagulopathy	14.6	12.6	0.241	13.5	11.5	0.075	14.4	10.8	0.001	14.1	11.3	<.0001	12.0
Obesity	15.7	13.8	0.271	16.6	15.9	0.575	19.4	17.9	0.272	17.4	16.6	0.369	16.8
Weight loss	8.4	9.2	0.590	8.9	7.3	0.084	7.8	6.7	0.204	8.4	7.2	0.041	7.5
Fluid and electrolyte disorders	52.4	45.1	0.003	46.2	38.8	<.0001	37.4	29.7	<.0001	44.6	34.9	<.0001	37.5
Blood loss anemia	5.7	4.0	0.115	4.1	3.3	0.203	2.4	2.0	0.447	3.9	2.7	0.002	3.0
Deficiency anemias	63.3	55.7	0.002	47.0	43.1	0.027	36.9	32.6	0.010	47.5	39.3	<.0001	41.5
Alcohol abuse	6.5	5.6	0.442	6.6	7.1	0.606	9.2	8.4	0.440	7.5	7.6	0.900	7.6
Drug abuse	2.6	3.2	0.516	3.3	3.6	0.735	3.3	4.6	0.075	3.2	4.0	0.034	3.8
Psychoses	6.5	7.1	0.642	7.9	7.7	0.883	9.9	8.3	0.117	8.2	8.0	0.633	8.0
Depression	16.3	15.3	0.579	17.1	16.8	0.863	21.0	17.3	0.006	18.3	16.9	0.088	17.3

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor blocker; BP, blood pressure; VA, Veterans Affairs; eGFR, estimated glomerular filtration rate

P-values reported for t-tests of continuous variables and chi-square tests for categorical variables for each ACEI/ARB comparison within eGFR category

a Race values do not add up to 100% due to unknown race (<1%)

b Potential contraindications to ACEIs include: pregnancy, renal artery stenosis, angioedema, hypotension, systolic BP < 85mmHg, serum potassium > 5.5 mEq/L, or creatinine clearance < 30 ml/min

c Comorbid conditions include a total of 28 Elixhauser comorbid conditions with cardiac arrhythmias

Table 2-2. Characteristics of Propensity-Matched Patients Hospitalized for Heart Failure with LVEF <40%, According to Baseline eGFR Category (n=4,224)

		Baseline Estimated Glomerular Filtration Rate (ml/min/1.73m^2)							
		15-29		30-44		45-59		Overall	
Baseline Characteristic		n=942	Standard Difference	n=1,686	Standard Difference	n=1,596	Standard Difference	n=4,224	Standard Difference
Age at index date, mean (SD), years		73.8 (10.6)	1.2	74.7 (10)	1.0	71.5 (10.9)	2.5	73.3 (10.6)	1.6
Female sex, %		0.6	0.0	0.8	2.6	1.6	3.0	1.1	0.5
Race, %[a]									
	White	73.8	0.5	76.5	4.2	70.8	3.9	73.7	0.0
	Black	18.3	2.2	16.9	1.6	20.4	1.9	18.5	0.6
	Other	8.0	2.4	6.5	3.8	8.5	4.5	7.6	0.2
Married, %		50.9	0.4	53.4	6.7	49.4	1.3	51.3	3.2
Any service-connected disability, %		30.5	5.1	30.7	1.8	29.5	1.6	30.2	0.2
Required copayment, %		10.6	2.8	11.3	2.6	11.3	4.0	11.2	3.2
Previous ACEI or ARB therapy, %		48.5	2.1	51.5	0.9	53.3	5.3	51.5	1.9
Contraindications to ACEI therapy, %[b]		25.2	4.4	23.7	0.0	20.7	0.9	22.9	0.7
Laboratory values, mean (SD)									
	Baseline serum creatinine, mg/dL	2.7 (0.5)	1.2	1.8 (0.2)	0.2	1.4 (0.2)	0.1	1.8 (0.6)	0.3
	Baseline eGFR, mL/min/1.73m^2	24 (4)	1.1	37.6 (4.3)	0.8	52.2 (4.3)	0.7	40.1 (11.6)	0.1
	Admission serum creatinine, mg/dL	2.6 (0.7)	1.2	1.8 (0.4)	5.2	1.4 (0.3)	1.7	1.8 (0.6)	1.3
	Blood urea nitrogen, mg/dL	51.4 (22.7)	2.6	36.4 (14.8)	4.4	27.7 (11.2)	2.0	36.5 (18.1)	2.6
	Hematocrit, %	33.8 (5.3)	7.1	35.9 (5.5)	3.2	37.5 (5.3)	0.8	36 (5.6)	2.5
	Serum sodium, mEq/L	138.4 (3.9)	2.6	138.2 (3.8)	1.7	138 (3.9)	0.3	138.1 (3.8)	1.4
	Serum potassium, mEq/L	4.2 (0.6)	7.7	4.1 (0.5)	1.3	4 (0.5)	0.2	4 (0.6)	1.4
	Systolic BP, mmHg	133.5 (26)	4.4	129.3 (23.6)	0.0	128.8 (23.1)	0.2	130 (24)	1.1

	Diastolic BP, mmHg	73.7 (16.2)	0.6	72.2 (15.1)	3.7	74.2 (15.2)	4.1	73.3 (15.4)	2.8
	Mean BP, mmHg	93.7 (17.7)	2.5	91.2 (16.1)	2.3	92.4 (16)	2.5	92.2 (16.5)	1.2
	Pulse, beats/minute	79.8 (18)	0.7	80.3 (17.6)	3.0	82.5 (18.3)	1.2	81 (18)	1.8
	Body mass index, kg/m^2	28.7 (6.3)	2.0	28.9 (6.3)	3.0	29.1 (6.8)	0.5	28.9 (6.5)	0.9
Discharge medication use, %									
	Anti-arrhythmic drugs	7.6	0.0	7.8	2.2	6.2	1.6	7.2	0.4
	Anticoagulants	41.6	0.9	40.0	2.9	39.2	2.1	40.1	2.1
	Aspirin	50.7	2.5	41.9	1.0	42.2	4.8	44.0	1.6
	β-blockers	72.3	1.4	61.3	1.7	60.6	1.3	63.5	0.1
	Calcium channel blockers	17.7	0.6	10.7	2.3	9.5	4.3	11.8	2.2
	Digoxin	22.1	3.1	23.8	0.6	28.0	0.8	25.0	1.2
	Loop diuretics	82.9	2.8	76.3	0.3	76.4	4.1	77.8	0.9
	Potassium-sparing diuretics	13.5	0.6	15.5	0.7	20.7	0.6	17.0	0.4
	Other diuretics	10.0	0.0	8.1	1.3	8.1	3.2	8.5	1.7
	Hydralazine	28.2	0.9	15.5	2.0	10.5	0.8	16.5	0.8
	Nitrates	47.2	1.3	36.3	0.5	30.4	0.8	36.5	0.2
History of cardiovascular disease, %									
	Previous heart failure hospitalization	36.9	0.9	31.2	1.0	26.6	3.4	30.7	1.8
	Coronary artery disease	87.4	0.6	84.8	5.0	82.0	1.0	84.3	1.4
	Acute myocardial infarction	49.5	5.9	49.2	0.2	47.9	1.5	48.8	2.0
	Angina	25.0	3.4	25.1	1.9	25.6	1.7	25.2	0.7
	Atrial fibrillation	41.3	3.0	46.9	3.3	45.5	0.0	45.1	2.0
	Percutaneous intervention	7.2	1.6	6.2	4.4	6.6	1.0	6.6	1.7
	Coronary artery bypass grafting	2.0	1.5	2.3	0.8	3.0	0.0	2.5	0.6
	Pacemaker/defibrillator	29.4	1.4	29.6	1.3	27.3	1.1	28.7	0.6
Fiscal year of index admission, mean (SD)		2005.3 (1.4)	0.5	2005.3 (1.3)	4.9	2005.3 (1.4)	2.4	2005.3 (1.4)	0.9
VA Medical Center Census Region, %									
	Northeast	15.5	3.5	12.5	0.4	10.7	1.6	12.5	0.1
	Midwest	24.7	4.4	24.1	0.8	25.1	2.6	24.6	0.3

	South	42.1	1.3	44.7	3.1	44.3	0.8	44.0	0.7
	West	16.0	0.6	17.2	2.5	17.6	1.6	17.1	0.3
	Outside Census Regions	1.6	1.7	1.5	2.9	2.3	2.5	1.8	0.4
Length of index hospital stay, days, mean (SD)		6.7 (9.2)	2.1	5.9 (6.1)	3.8	5.5 (5.4)	2.7	5.9 (6.7)	1.2
Admission to long-term care, %		16.0	6.4	15.7	3.9	12.8	0.8	14.7	2.8
Use of non-VA outpatient services, %		29.8	7.0	27.8	3.4	23.8	1.8	26.8	0.4
Number of comorbid conditions, mean (SD)[c]		5.8 (2.3)	2.3	5.6 (2.4)	1.4	5.1 (2.4)	4.3	5.4 (2.4)	0.6
Comorbid conditions, %[c]									
	Cardiac arrhythmias	25.0	0.5	28.4	3.4	29.0	1.4	27.9	1.8
	Valvular disease	29.8	4.2	32.9	0.0	29.5	0.8	30.9	0.6
	Pulmonary circulation disorders	13.1	1.9	16.2	1.6	13.9	0.7	14.6	0.5
	Peripheral vascular disease	35.4	2.2	30.6	4.9	26.1	1.4	30.0	0.9
	Hypertension	94.3	0.0	92.0	3.1	88.8	0.4	91.3	1.3
	Paralysis	4.9	0.0	4.3	3.5	4.1	0.6	4.3	1.2
	Other neurological	6.7	2.5	5.9	2.0	6.6	1.0	6.4	0.6
	Chronic pulmonary disease	46.0	4.7	50.8	5.7	46.9	3.8	48.3	0.2
	Diabetes (uncomplicated)	20.0	1.1	25.6	3.0	31.0	5.1	26.4	3.0
	Diabetes (complicated)	42.0	3.4	30.4	3.6	21.1	4.3	29.5	2.1
	Hypothyroidism	15.8	1.7	18.3	5.2	13.7	1.8	16.0	2.5
	Liver disease	3.5	3.5	4.7	0.6	4.0	3.8	4.2	2.4
	Peptic ulcer disease	0.2	0.0	0.4	1.8	0.3	6.7	0.3	1.6
	AIDS/HIV	0.3	3.8	0.0	0.0	0.4	0.0	0.2	1.0
	Lymphoma	0.7	2.5	1.0	0.0	1.4	2.1	1.1	0.5
	Metastatic cancer	0.6	5.3	1.4	0.0	1.4	0.0	1.2	0.9
	Solid tumor without metastasis	12.2	1.9	14.2	2.7	12.8	3.0	13.2	0.4
	Rheumatoid arthritis/collagen vascular diseases	2.2	1.4	2.5	0.0	2.8	1.5	2.5	0.3
	Coagulopathy	13.4	2.5	12.8	1.4	13.9	2.5	13.3	1.0
	Obesity	14.5	3.0	17.3	6.3	17.4	0.3	16.7	3.0
	Weight loss	8.8	2.2	8.2	0.4	7.3	1.0	8.0	1.0
	Fluid and electrolyte disorders	50.0	2.1	44.5	1.9	35.1	2.6	42.2	0.3
	Blood loss anemia	5.4	2.8	4.2	0.6	2.4	1.6	3.8	0.0

	Deficiency anemias	61.8	4.4	47.2	3.1	35.3	1.8	45.9	1.5
	Alcohol abuse	5.5	3.7	6.6	3.3	8.6	8.5	7.1	5.5
	Drug abuse	2.4	1.4	3.3	1.3	3.5	4.1	3.2	1.3
	Psychoses	6.2	5.3	7.7	2.2	9.9	5.0	8.2	1.9
	Depression	14.5	4.2	17.4	3.4	20.9	0.6	18.1	0.7

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor blocker; BP, blood pressure; VA, Veterans Affairs; eGFR, estimated glomerular filtration rate

Absolute standardized difference (percentile) in covariate means and proportions after matching according to receipt of ACEI/ARB by eGFR category

[a] Race values do not add up to 100% due to unknown race (<1%)

[b] Potential contraindications to ACEIs include: pregnancy, renal artery stenosis, angioedema, hypotension, systolic BP < 85mmHg, serum potassium > 5.5 mEq/L, or creatinine clearance < 30 ml/min

[c] Comorbid conditions include a total of 28 Elixhauser comorbid conditions with cardiac arrhythmias

Table 2-3. Outcomes by ACEI or ARB Therapy at Discharge among Patients Hospitalized for Heart Failure with LVEF <40% According to Baseline Estimated Glomerular Filtration Rate

Outcome		Baseline Estimated Glomerular Filtration Rate (ml/min/1.73m^2)					
		15-29		30-44		45-59	
		Events (%)		Events (%)		Events (%)	
		No ACEI/ ARB	ACEI/ ARB	No ACEI/ ARB	ACEI/ ARB	No ACEI/ ARB	ACEI/ ARB
All-cause mortality							
	Overall	326 (45.0)	384 (40.5)	463 (42.9)	973 (33.6)	304 (29.8)	954 (24.1)
	Propensity-matched	211 (44.8)	211 (44.8)	355 (42.1)	317 (37.6)	228 (28.6)	215 (26.9)
Heart failure re-hospitalization							
	Overall	404 (55.7)	528 (55.6)	575 (53.3)	1453 (50.2)	515 (50.4)	1835 (46.4)
	Propensity-matched	272 (57.8)	249 (52.9)	456 (54.1)	421 (49.9)	405 (50.8)	365 (45.7)
End stage renal disease or doubling of serum creatinine							
	Overall	154 (21.2)	162 (17.1)	100 (9.3)	231 (8.0)	91 (8.9)	295 (7.5)
	Propensity-matched	91 (19.3)	94 (20.0)	74 (8.8)	69 (8.2)	75 (9.4)	54 (6.8)

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor blocker; LVEF, left ventricular ejection fraction

Table 2-4. Results of Cox Proportional Hazards Regression Models for ACEI or ARB Therapy at Discharge among Propensity-Matched Patients Hospitalized for Heart Failure with LVEF <40% According to Baseline Estimated Glomerular Filtration Rate

	Baseline Estimated Glomerular Filtration Rate (ml/min/1.73m^2)		
	15-29	**30-44**	**45-59**
Outcomes	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
All-cause mortality	0.95 (0.77, 1.18)	0.83 (0.70, 0.98)	1.01 (0.82, 1.23)
Heart failure rehospitalization	0.80 (0.64, 0.99)	0.80 (0.68, 0.94)	0.81 (0.68, 0.96)
End stage renal disease or doubling of serum creatinine	1.05 (0.78, 1.42)	0.90 (0.65, 1.26)	0.73 (0.51, 1.04)
Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor blocker; LVEF, left ventricular ejection fraction; CI, confidence interval			

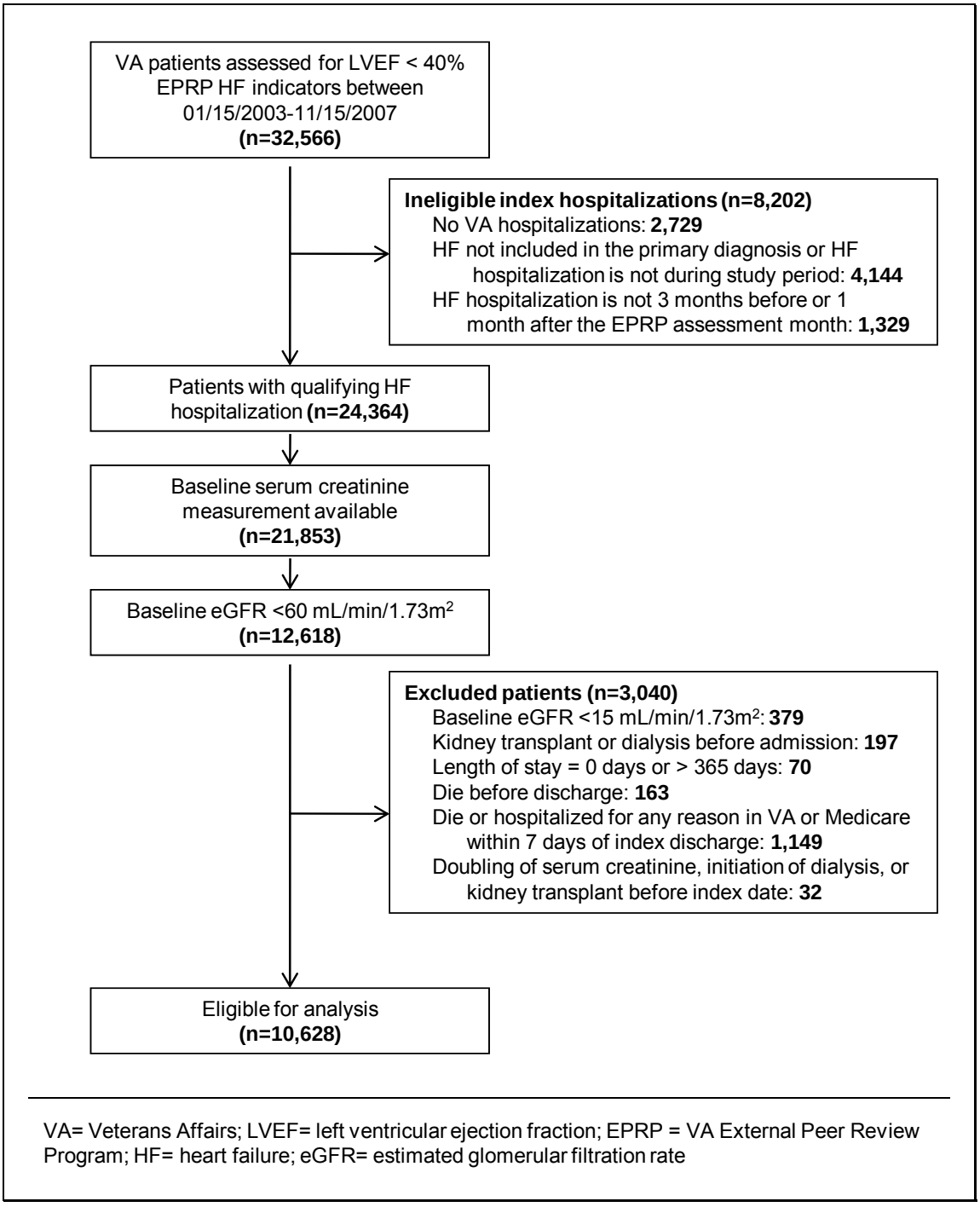

Figure 2-1. Selection of Study Cohort

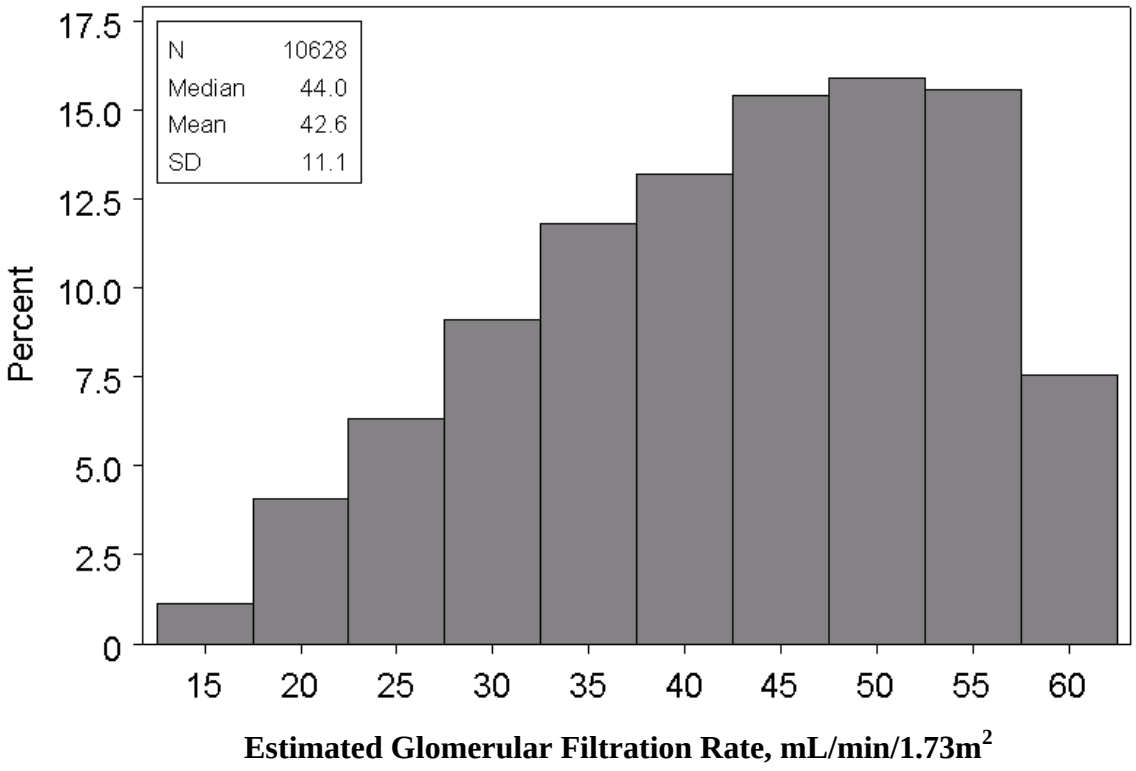

Figure 2-2. Distribution of Baseline Estimated Glomerular Filtration Rate in the Study Population

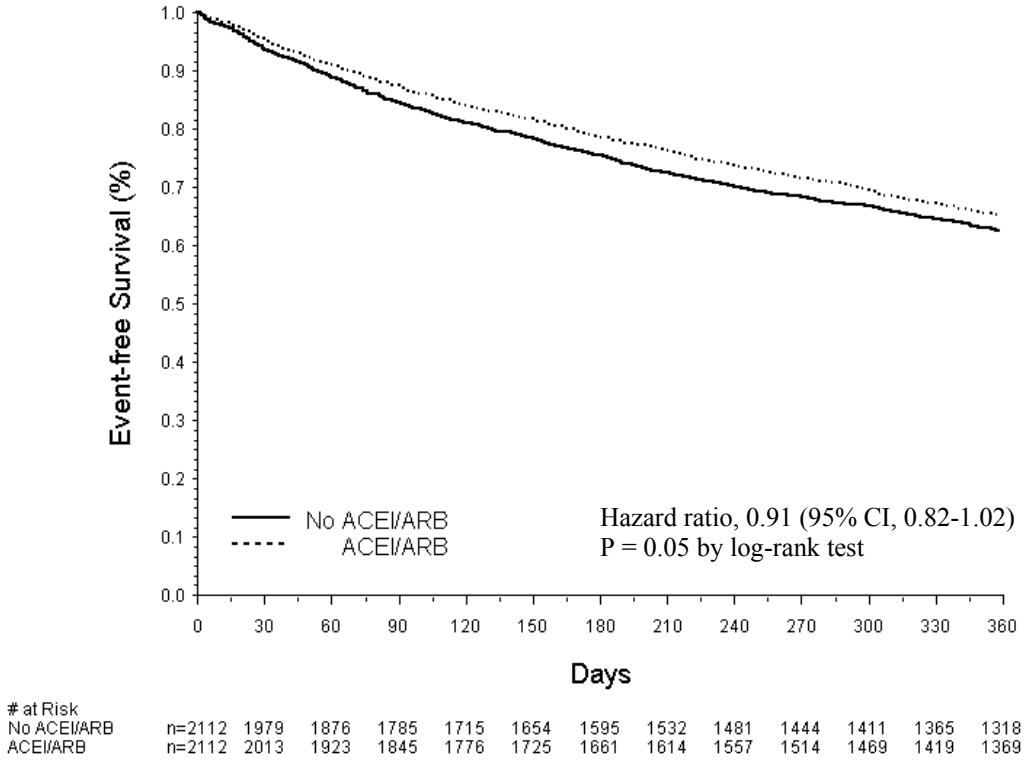

Figure 2-3. Kaplan-Meier Survival Estimates of All-Cause Mortality According to Receipt of ACEI or ARB at Discharge among Patients Hospitalized for Heart Failure with LVEF <40% with Estimated Glomerular Filtration Rate <60 mL/min/1.73m^2

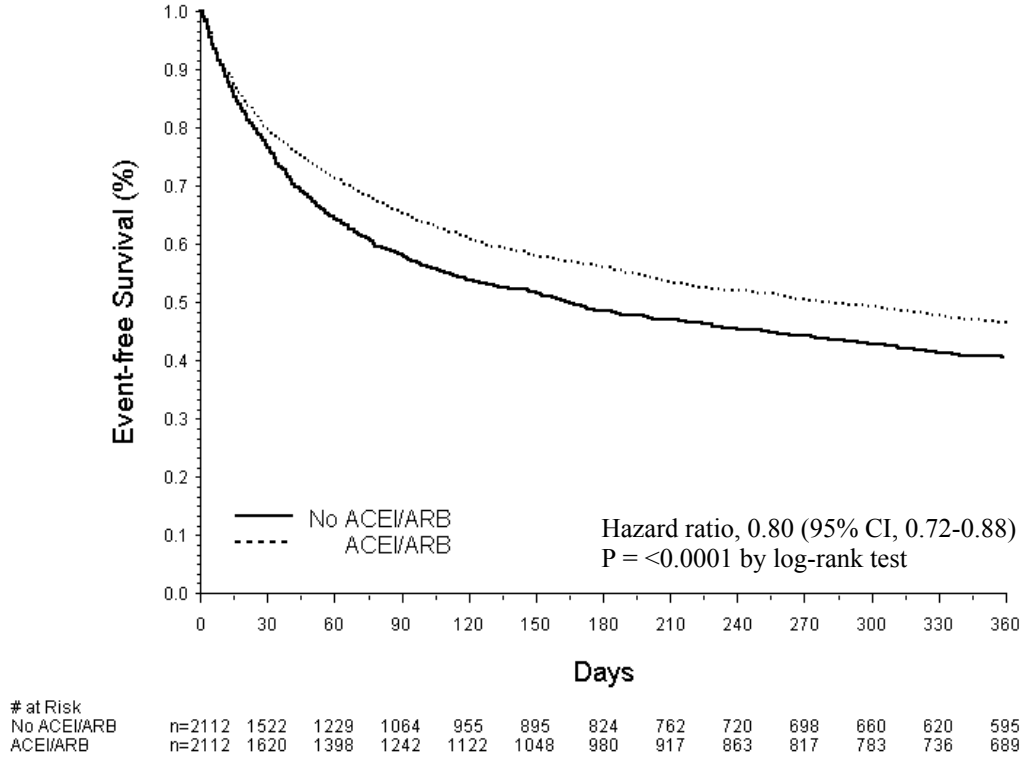

Figure 2-4. Kaplan-Meier Survival Estimates of Rehospitalization for Heart Failure According to Receipt of ACEI or ARB at Discharge among Patients Hospitalized for Heart Failure with LVEF <40% with Estimated Glomerular Filtration Rate <60 mL/min/1.73m^2

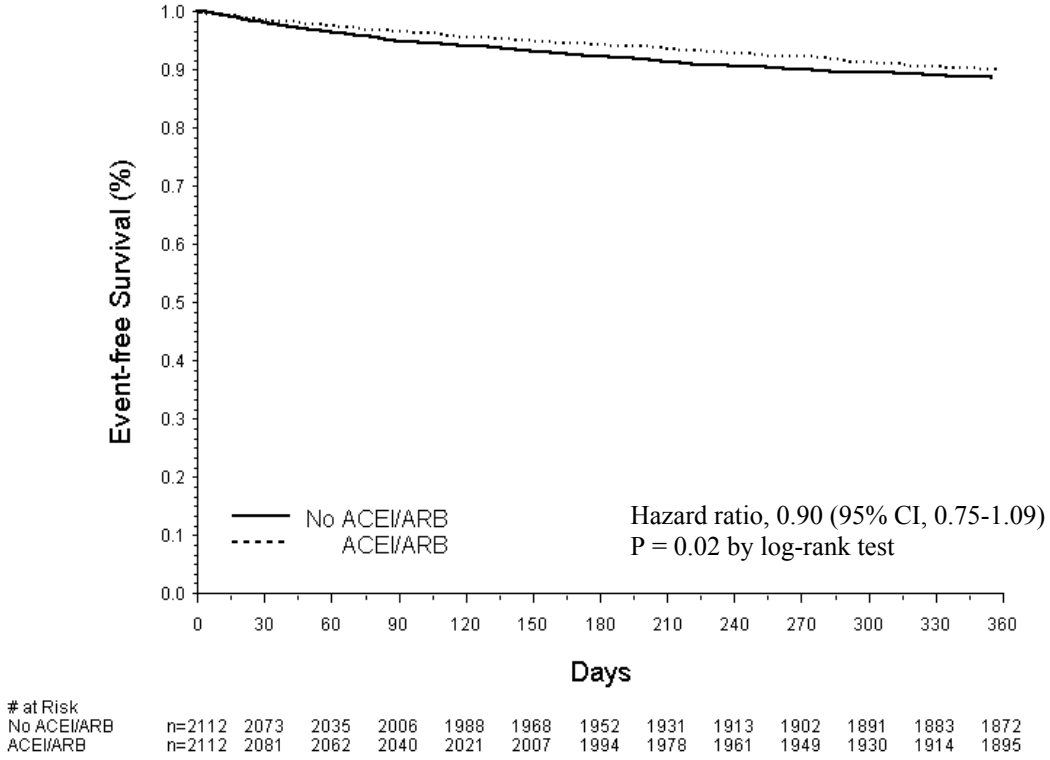

Figure 2-5. Kaplan-Meier Survival Estimates of End Stage Renal Disease or Doubling of Serum Creatinine According to Receipt of ACEI or ARB at Discharge among Patients Hospitalized for Heart Failure with LVEF <40% with Estimated Glomerular Filtration Rate <60 mL/min/1.73m^2

CHAPTER 3 :
THE EFFECT OF TREATMENT WITH NON-DIHYDROPYRIDINE CALCIUM CHANNEL BLOCKERS AMONG PATIENTS WITH SUPRAVENTRICULAR TACHYARRHYTHMIAS HOSPITALIZED FOR HEART FAILURE WITH LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

Abstract

Background: Non-dihydropyridine calcium channel blockers (diltiazem and verapamil) are used to control ventricular rate among patients with supraventricular tachyarrhythmias. However, there are concerns about the safety of non-dihydropyridine calcium channel blockers in heart failure patients with left ventricular systolic dysfunction, among whom supraventricular tachyarrhythmias are common. We investigated whether receipt of a non-dihydropyridine calcium channel blocker at discharge among patients with both conditions was associated with worse patient outcomes.

Methods: Patients with atrial fibrillation, atrial flutter, or paroxysmal supraventricular tachyarrhythmias hospitalized for heart failure with left ventricular ejection fraction <40% at a Veterans Affairs Medical Center between 2003 and 2007 were matched on propensity scores according to the receipt of diltiazem or verapamil at discharge. Cox proportional hazards models were used to evaluate the association between non-dihydropyridine calcium channel blocker use at discharge, all-cause mortality, and rehospitalization for heart failure at six months among propensity-matched patients, and the Kaplan–Meier method was used to estimate survival.

Results: A total of 8,732 patients were included in the study. We matched 467 of 470 patients who received a non-dihydropyridine calcium channel blocker at discharge with up to 3 patients who did not receive a calcium channel blocker at discharge for a total of 1,791 matched patients. After six months, patients who received diltiazem or verapamil at discharge had a 27% lower risk of all-cause mortality compared with patients who did not receive a calcium channel blocker at discharge (hazard ratio [HR] 0.73; 95% CI: 0.55-

0.96; log-rank P=0.04). Although the rate of heart failure rehospitalization at six months was lower for non-dihydropyridine calcium channel blocker recipients (34.7% vs 36.4%), the difference was not statistically significant (HR, 0.95; 95% CI: 0.79-1.15; log-rank P=0.42).

Conclusions: In this study of veterans with supraventricular tachyarrhythmias hospitalized for heart failure with left ventricular systolic dysfunction, among whom concomitant therapy with renin-angiotensin inhibitors and β-blockers was common, receipt of diltiazem or verapamil at discharge was associated with a lower risk of mortality at six months and was not associated with heart failure rehospitalization. Non-dihydropyridine calcium channel blockers appear to be safe and potentially beneficial when used in conjunction with these heart failure therapies.

Introduction

Non-dihydropyridine (DHP) calcium channel blockers (CCBs), comprised of diltiazem and verapamil, are distinguished from other calcium channel antagonists by their ability to slow myocardial contractility and atrioventricular node conduction. Although cardiac arrhythmias are a common finding among patients with heart failure (HF) and increase alongside severity of HF,[71] the safety and efficacy of non-DHP CCBs for the treatment of certain cardiac arrhythmias among patients with HF with left ventricular (LV) dysfunction remains a concern. In some small studies and early clinical trials, non-DHP CCBs were associated with increased risk of mortality and worsening HF when used in patients with HF with reduced left ventricular ejection fraction (LVEF).[72-76] However, more recent studies found both neutral and beneficial effects of non-DHP

CCBs in this population, particularly when used in conjunction with a renin-angiotensin system inhibitor.[77-86] The experience with non-DHP CCBs is more limited among patients with both HF with LV dysfunction and supraventricular tachyarrhythmias, including atrial fibrillation and flutter, for whom non-DHP CCBs have a clinical application as antiarrhythmic therapy.

The purpose of our study, therefore, was to evaluate whether the receipt of diltiazem or verapamil at discharge among a cohort of veterans with atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia hospitalized for HF with reduced LVEF was associated with increased risk of mortality or rehospitalization for HF. In contrast with previous studies, we examine this question exclusively among patients with supraventricular tachyarrhythmias with HF with LVSD at hospital discharge in the contemporary setting of background renin-angiotensin system inhibitor and β-adrenergic receptor blocker therapy.

Methods

Study Design

Veterans age 18 years or older who were hospitalized for HF with LVEF < 40% at a VA medical center between January 15, 2003 and November 15, 2007 were identified using data from the VA External Peer Review Program (EPRP). The VA's Office of Quality and Performance contracts trained medical reviewers to abstract charts from a random nationwide sample of veterans in the EPRP to evaluate the quality of care delivered by VA facilities according to evidence-based performance measures. The EPRP sampling frame includes all VA beneficiaries with at least two years of continuous

enrollment and who had at least one VA outpatient visit or hospitalization in the year prior to the assessment period. [16, 17]

Participants

Patients were identified using three EPRP performance measures for ACEI/ARB use among HF patients with LVEF < 40%. To be eligible for these measures, patients must have a principal discharge diagnosis of HF and chart documentation of LVEF <40% or a narrative description of moderate or severe left systolic dysfunction. Exclusion criteria for these measures included allergy to both an ACEI and ARB, moderate or severe renal artery stenosis, participation in a clinical trial, and transfer to another hospital or hospice care.[18] For patients with multiple EPRP assessments (7,203/32,566; 22%), we used the earliest inpatient assessment during the study period. Because the EPRP data does not specify the episode of care assessed, we selected the closest VA HF hospitalization up to three months before or one month after their EPRP assessment date. We defined hospitalization for HF using *International Classification of Diseases, Ninth Revision* [*ICD-9-CM*] codes in the patient's primary diagnosis: 428.0 (congestive HF, unspecified), 428.1 (left HF); 428.2 (systolic HF) which is unspecified (428.20), acute (428.21), chronic (428.22), or acute or chronic (428.23); 428.3 (diastolic HF) which is unspecified (428.30), acute (428.31), chronic (428.32), or acute or chronic (428.33); 428.4 (combined systolic and diastolic HF), which is unspecified (428.40), acute (428.41), chronic (428.42), or acute or chronic (428.43); 428.9 (HF, unspecified); 398.91 (rheumatic HF); 402.01, 402.11, or 402.91 (hypertensive heart disease with HF); and 404.01, 404.03, 404.11, 404.13, 404.91, or 404.93 (hypertensive heart disease and

chronic kidney disease with HF). Same-day readmissions for HF were treated as a single hospital stay. To be eligible for inclusion in the study, patients were required to have comorbid supraventricular tachyarrhythmias, defined by the presence of ICD-9-CM codes for atrial fibrillation (427.31), atrial flutter (427.32), and paroxysmal supraventricular tachycardia (427.0) among the patient's administrative claims during the two years before admission or by a secondary diagnosis from the patient's index HF hospitalization. A flow diagram of study inclusion and exclusion criteria is illustrated in **Figure 3-1**.

Sources of Data

We used multiple VA databases to evaluate patient characteristics and outcomes. Information about inpatient and outpatient visits was obtained from the VA National Patient Care Database. Laboratory results and medication information were obtained from VA Decision Support System records. [19, 20] To account for use of Medicare services during the study period, we used data from the VA/CMS Data for Research project.[21] We ascertained a patient's vital status by combining the VA Beneficiary Identification and Record Locator Subsystem dataset with VA/CMS data linked to Medicare's Enrollment Database.

Exposure Definitions

We defined exposure to a non-DHP CCB by the receipt of verapamil or diltiazem on the final day of a patient's inpatient stay or by an outpatient fill within seven days of a patient's index discharge from the index hospitalization. [22, 23]

Study Outcomes

The primary outcome was all-cause mortality within six months of the patient's index date. Because cause of death was not specified in the VA or Medicare vital status datasets, we could not identify the specific cause of death. Our secondary outcome was rehospitalization for HF within six months in the VA or Medicare. Patients who did not die were censored on May 15, 2008, six months after the last EPRP assessment month for which we had complete information. The index date of observation for all patients is seven days after discharge from the patient's index HF hospitalization to identify patients who filled discharge medications on an outpatient basis.

Patient Characteristics/Covariates

Patient sociodemographic characteristics included the presence of any service-connected disability, medication copayments using the VA means test indicator, and marital status. We used the most frequent value of self-identified patient race from inpatient and outpatient records and categorized patients as white, black (including Non-Hispanic Black or African American), or other (including Hispanic or Latino, American

Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander).[24] For patients whose race could not be determined from the VA datasets (n=779), we substituted race, when available, from the VA/CMS Vital Status dataset. We assigned the VA Medical Center that provided treatment to U.S. Census Regions. We also examined health care utilization characteristics, including length of the index hospital stay and admission to long-term care up to 6 months before admission and during follow up. We used VA/CMS Medicare outpatient claims to identify whether patients sought care outside the VA during the study period.

We obtained laboratory, vital sign information, and demographic characteristics reported at admission. Body mass index (BMI) was calculated from the patient's weight up to six months before admission and height recorded at any time. We examined two-year history of HF hospitalization, coronary artery disease, including acute myocardial infarction (AMI), angina, percutaneous coronary intervention (PCI), coronary bypass grafting (CABG), stroke or transient ischemic attack, and the presence of a pacemaker or implantable defibrillator. We also examined concomitant use of other HF therapies at discharge.

We assessed patients for the presence of potential contraindications to treatment with CCBs, which included sick sinus rhythm or advanced atrioventricular block without a pacemaker, or a diagnosis of hypotension using inpatient and outpatient claims from the two years before the index admission; or systolic blood pressure < 85 mmHg at admission.[87] Comorbid conditions were identified from VA and Medicare inpatient and outpatient claims from the two years prior to index hospitalization using 28 revised conditions (excluding comorbid HF) from the Elixhauser Comorbidity Index software

available on the Agency for Healthcare Research and Quality (AHRQ) website. A patient's total number of comorbidities was included as an additional covariate.

Statistical Analyses

Missing values for potential confounders including hematocrit (6.4%), serum creatinine (7.0%), BMI (4.0%), and sodium, potassium, systolic blood pressure, diastolic blood pressure, and pulse, which were missing in 1-2% of the overall sample, were imputed using mean values from 10 imputed datasets. Missing values of hematocrit were estimated with hemoglobin values (hemoglobin x 3) when available.[27].

To address between-patient variation not adequately controlled with standard multivariable approaches, we used propensity score methods.[28-30] Because patients were not randomly assigned to receive non-DHP CCB therapy, we performed propensity-score matching to account for potential confounding and selection bias. The probability of receiving either diltiazem or verapamil at discharge was modeled using a multivariable logistic regression model including all Table 3-1 covariates. The c statistic for this model was 0.788, which indicated strong ability to discriminate between non-DHP CCB recipients and non-recipients. Patients were then 1:1 matched within category according to the modeled propensity score using an iterative Greedy 5-to-1 digit matching algorithm.[66] We repeated this algorithm three times without replacement to select up to three controls per non-DHP CCB recipient. The distribution of patient characteristics before and after matching according to non-DHP CCB receipt was compared using absolute standardized differences, expressed as percentages, in covariate means and

proportions (with a ≤10% threshold) to assess the success of matching in balancing potential confounders.[37, 39]

Time-to-event curves were estimated using the Kaplan–Meier method according to receipt of a non-DHP CCB at discharge and compared using a log-rank test. Survival time was measured as the number of days between the index date until the outcome of interest or May 15, 2008. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for both outcomes according to the receipt of non-DHP CCB therapy. We confirmed the appropriateness of the proportional hazards assumption for each model using Martingale residuals.

Additional Sensitivity Analyses

We performed two sensitivity analyses to examine the degree to which potential exposure misclassification of non-DHP CCB users could affect our findings. In our original sample, we observed 349 patients did not receive a non-DHP CCB at discharge, but filled a prescription for a non-DHP CCB in the 90 days prior to their index HF hospitalization. In our first sensitivity analysis, we considered these patients as eligible controls and added them to the sample of patients who did not receive a non-DHP CCB at discharge. We repeated propensity-score matching but included a binary variable to reflect non-DHP CCB use before admission in our propensity score model. The c-statistic for this model was 0.88. We matched 446 of 470 non-DHP users to up to three controls for a total of 1,450 patients.

In our second sensitivity analysis, we added the 349 prior non-DHP CCB users to our group of patients who received a non-DHP CCB at discharge for a total of 819

patients in this group. We used the original propensity score model from our main analysis which did not include a variable for prior non-DHP use. The c-statistic for the model in this analysis was 0.74. We matched all 819 patients considered to have non-DHP exposure in this analysis with up to three control patients for a total of 3,113 patients.

All analyses were performed with SAS 9.2 (SAS Institute, Cary, NC). The Providence VA Medical Center institutional review board approved the study protocol.

Results

Between January 15, 2003, and November 15, 2007, there were 24,364 patients assessed for VA quality measures for HF with LVEF <0.40 for whom we identified an eligible HF hospitalization at 120 VA medical centers nationwide. Of these, 10,926 patients (44.8%) had atrial fibrillation, atrial flutter, or paroxysmal supraventricular tachycardia during the two years prior to admission, or as a secondary diagnosis for the patient's index HF hospitalization. (**Figure 3-1**) We excluded 168 patients who died before discharge, 1,057 patients who died or were rehospitalized for any reason within 7 days of discharge from their index hospitalization, 33 patients who had a length of stay greater than one year or less than one day, and 2 patients for whom we were missing all clinical data. Of the remaining patients, we excluded 9 patients who received both DHP and non-DHP CCBs at discharge, 576 patients who received a DHP CCB at discharge, and 349 patients who did not receive any CCB at discharge, but had filled a prescription for a non-DHP CCB in the 90 days prior to their index HF hospitalization. Of the 8,732 patients included in our study, 442 received diltiazem and 28 received verapamil at

discharge. The baseline characteristics of patients before propensity-score matching according to receipt of a non-DHP CCB at hospital discharge are shown in **Table 3-1**.

The mean age of patients before propensity-score matching was 72.3 years, almost all patients were male (99.1%), and 77.1% were white. Over 80% of patients had a history of coronary artery disease or hypertension, 29.7% were previously hospitalized for HF, and 15.3% had a history of ischemic stroke or transient ischemic attack. The rate of use of concomitant HF therapies at discharge was high, with 67.5% receiving angiotensin-converting enzyme inhibitors, 7.5% receiving angiotensin-receptor blockers, and 72.1% receiving β-blockers. Standardized differences > 10% before matching indicated important differences in baseline characteristics. Compared with those who did not receive a CCB, patients receiving a non-DHP CCB were younger, had higher mean systolic and diastolic blood pressure, were less likely to have a history of coronary artery disease, acute myocardial infarction, or comorbid anemia, and had higher estimated renal function and hematocrit. Prior coronary revascularization was more common among patients who did not receive a non-DHP CCB at discharge as well as the presence of a pacemaker or defibrillator. These patients were also more likely to receive other antiarrhythmic therapy, β-blockers, and potassium-sparing diuretics at discharge and use outpatient services outside the VA health care system. The unadjusted rate of all-cause mortality at six months was 14.0% among patients who received a non-DHP CCB compared with 20.5% of patients not treated with a CCB. Fewer patients who received a non-DHP CCB were rehospitalized for HF within six months compared with patients who did not receive a CCB (34.5% versus 41.5%).

We matched 467 patients (99%) who received a non-DHP CCB at discharge with up to three controls with a similar probability of receiving a non-DHP CCB at discharge for a total of 1,791 matched patients. The characteristics of propensity-matched patients included in the propensity score model are presented in **Table 3-1**. Standardized differences for all measured characteristics were < 10%, indicating improved balance between patients who received a non-DHP CCB and those who did not in terms of observed confounders. The mean age of propensity-matched patients was 70.4 years, 59.6% had comorbid chronic obstructive pulmonary disease, and the majority of patients received concomitant angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, anticoagulants, β-blockers, and loop diuretics.

After propensity-score matching, 309 patients (17.3%) died and 644 (36.0%) were rehospitalized for HF within 6 months of the index date. All-cause mortality within 6 months was lower among patients who received a non-DHP CCB compared to matched patients who did not receive a non-DHP CCB (14.1% versus 18.4%). Similarly, 34.7% of non-DHP CCB recipients were rehospitalized for HF within 6 months compared to 36.4% of matched patients who did not receive a non-DHP CCB. Kaplan-Meier cumulative incidence estimates of mortality and rehospitalization for HF among propensity-matched patients are presented in **Figures 3-2 and 3-3**. Receipt of a non-DHP CCB at discharge was associated with a reduction in the risk of all-cause mortality within 6 months compared with those who did not receive a CCB at discharge. (HR: 0.73; 95% CI: 0.55-0.96; log-rank P=0.04). Our Cox proportional hazards model and Kaplan–Meier plot showed a nonsignificant reduction in the risk of HF rehospitalization within 6 months

between patients who received a non-DHP CCB at discharge and those who did not (HR: 0.95; 95% CI: 0.79-1.15; log-rank P=0.42).

In our first sensitivity analyses, where patients who had received a non-DHP CCB prior to admission but did not receive a non-DHP CCB at discharge were added back to the sample of patients who did not receive a non-DHP CCB at discharge, the reduction in mortality observed in our primary analysis was no longer statistically significant (**Table 3-2**). However, after reclassifying these patients as non-DHP CCB recipients, we observed a significant reduction in the risk of all-cause mortality among patients who received a non-DHP CCB at discharge compared to those who did not (HR: 0.79; 95% CI: 0.65-0.98; log-rank P= 0.03). In this sensitivity analysis, the association of non-DHP CCB use and risk of HF rehospitalization was unchanged from our main analysis (HR: 0.96; 95% CI: 0.84-1.10; log-rank P=0.55).

Discussion

In this retrospective cohort study of veterans with supraventricular tachyarrhythimas hospitalized for HF with reduced LVEF, among whom the majority received concomitant renin-angiotensin system inhibitor therapy, we did not find evidence of an increased risk of mortality or HF rehospitalization among patients who received a non-DHP CCB (either diltiazem or verapamil) at discharge. Instead, patients who received diltiazem or verapamil at discharge experienced a lower risk of mortality at six months when compared with patients who did not receive any CCB at discharge. In addition, we found no difference in the risk of rehospitalization for HF at six months between patients who received a non-DHP CCB at discharge and those who did not.

Patients with supraventricular tachyarrhythimas accounted for 42% of patients with eligible hospitalizations for HF with LVEF<40% in our original study population. The estimate is consistent with a previous report of the prevalence of atrial fibrillation among patients with severe HF.[88] Although only a small fraction of patients in the study population received either diltiazem or verapamil at discharge, we illustrate that these agents continue to be used in clinical practice among a patients with HF and reduced LVEF. Atrial fibrillation can exacerbate, as well as precipitate, HF by shortening diastolic filling time and reducing cardiac output in addition to impairing atrial contractile function.[71] Therefore, management of atrial tachyarrhythmia through pharmacologic control of ventricular rate or cardioversion can also improve HF-related outcomes.

The experience of non-DHP CCBs among patients with both supraventricular tachyarrhythimas and HF with reduced LVEF is limited. In a subgroup analysis of patients with atrial fibrillation enrolled in the Studies of Left Ventricular Dysfunction trials, CCB use was not associated with an increased risk of mortality among 333 patients with HF with LVEF ≤35%.[86] However, the type of CCB analyzed was unspecified. A few small studies which evaluated intravenous diltiazem in patients with atrial fibrillation and HF did not find an association with worsening HF, but an increase in incident hypotension.[81, 82].[89] Maragno *et al*. reported hemodynamic deterioration among two patients with HF following discontinuation of digoxin from combined diltiazem-digoxin therapy.[90] Intravenous and chronic oral administration of verapamil in 10 patients with chronic atrial fibrillation, among whom 6 patients had HF, improved ventricular response rates, but was associated with incident HF in 2 patients.[75]

More studies have evaluated non-DHP CCBs in the setting of HF with or without supraventricular tachyarrhythimas, but the findings from these studies have been limited and conflicting. In some small studies, patients with HF and reduced LVEF experienced hemodynamic deterioration when treated with verapamil[76], whereas administration with diltiazem was not associated with worsening HF.[77-79] In the Multicenter Diltiazem Postinfarction Trial (MDPIT), however, long-term diltiazem therapy was associated with and increased risk of cardiac events and mortality among patients with HF and LVEF <40%.[72, 73] In contrast, patients with HF and LVEF ≤30% in the Diltiazem in Dilated Cardiomyopathy Trial (DiDi) had improved cardiac function and a nonsignificant reduction in mortality and listing for heart transplantation.[80] Patients with HF in the Danish Verapamil Infarction Trial II (DAVIT II) did not experience an increase in mortality or cardiac events when treated with verapamil; however, the effect was not reported according to LVEF.[83] And combined verapamil and angiotensin-converting enzyme inhibitor therapy reduced the risk of cardiac events, including HF rehospitalization, among HF patients compared with angiotensin-converting enzyme monotherapy.[84, 85]

Differences in the use of adjunct HF therapies with non-DHP CCBs could account for the disparity in findings between studies. In MDPIT, over 50% of patients were treated with β-blockers while patients treated with β-blockers, as well as those with unstable or severe HF, were excluded from DAVIT II. In both studies, patients were not treated with renin-angiotensin system inhibitors. In the DiDi trial, as well as our study, the majority of patients received a renin-angiotensin system inhibitor in conjunction with diltiazem. The synergy between CCBs and renin-angiotensin system inhibitors has been

reported previously for hypertension and coronary artery disease.[91, 92] CCBs may enhance ACE-inhibitor induced vasodilation, while ACE-inhibitors have been shown to counteract peripheral edema associated with CCB therapy.

We considered the effects of potential misclassification of patients who received a non-DHP CCB in the 90 days before admission, but not at discharge from their index hospitalization. Because oral verapamil and diltiazem are used for the pharmacologic management of chronic atrial fibrillation, and most of these patients had received a 30 or 90-day supply of these medications before their index admission, it is possible that these patients were non-DHP CCB users who did not fill their medications until after our 7-day post-discharge exposure window. However, only 67 of 349 potentially misclassified patients received verapamil or diltiazem within 90 days of the index date. When these patients were included in the study as either non-DHP CCB recipients, we found a consistent reduction in the risk of 6-month all-cause mortality among patients receiving non-DHP CCBs. However, this effect was attenuated when these patients were included in the analysis as eligible controls.

The strengths of this study include a large, nationally-representative, sample of veterans for which we had comprehensive information on clinical measures and outcomes in both the VA and Medicare. Because of the sizable patient population included in the VA EPRP data, we were able to identify 470 patients with supraventricular tachyarrhythimas hospitalized for HF with LVEF <40% who received a non-DHP CCB at discharge, which is the largest number of patients among whom this study question has been examined to date. Additionally, we had a large population of HF patients with supraventricular tachyarrhythimas who were not treated with any CCB at

discharge from which to derive a propensity-matched sample, which improved our overall matching rate.

Our study also has many limitations. Because we did not have access to electronic medical records identifying discharge medications and used administrative pharmacy data, we utilized a proxy definition of medication receipt at discharge which considered the possibility that patients might fill a prescription for discharge medications on an outpatient basis. As a result, we extended the index date of our study to a week post-discharge to allow time for patients to obtain the study medications. [22] Although we were able to identify non-VA hospitalizations using VA/CMS data, we could not fully capture non-VA utilization among VA patients without Medicare. Indeed, only 59% of patients with qualifying VA HF hospitalizations (14,397/ 24,364) also had an inpatient or outpatient claim in the VA/CMS dataset and may have led us to underestimate HF rehospitalization and non-VA utilization. We also did not examine whether patients who received a non-DHP CCB at discharge adhered to the medication during follow-up. And although we simultaneously controlled for numerous covariates in our propensity score model, our study is not free from residual confounding by unmeasured covariates.

Conclusions

In conclusion, in veterans with supraventricular tachyarrhythimas hospitalized for HF with reduced ejection fraction, the majority of whom received a renin-angiotensin system inhibitor at discharge, the receipt of diltiazem or verapamil at discharge was associated with a reduction in the risk of all-cause mortality and was not associated with an increased risk of HF rehospitalization within 6 months. Our findings provide evidence

in support of a growing literature suggesting non-DHP CCBs could be a safe and viable choice for the management of supraventricular tachyarrhythmias among patients with HF and reduced LVEF.

Tables and Figures

Table 3-1. Baseline Demographic and Clinical Characteristics of Veterans Hospitalized for Heart Failure with Left Ventricular Ejection Fraction <40% According to Receipt of Non-Dihydropyridine Calcium Channel Blockers at Hospital Discharge, Before and After Matching

	Before Matching					After Matching			
Characteristic	**Non-DHP CCB** (N=470)	**No CCB** (N=8,262)	**Total** (N=8,732)	Standard Difference[a]		**Non-DHP CCB** (n=467)	**No CCB** (N=1,324)	**Total** (N=1,791)	Standard Difference[a]
Age at index date, years, mean (SD)	69.8 (11)	72.5 (10.5)	72.3 (10.5)	24.6		69.9 (11)	70.6 (11)	70.4 (11)	7.1
Female sex, %	1.7	0.9	0.9	7.4		1.5	1.6	1.6	0.7
Race, %[b]									
White	79.8	76.9	77.1	7.0		79.7	82.0	81.4	5.8
Black	12.8	16.4	16.2	10.3		12.9	11.9	12.2	2.8
Other	6.6	6.3	6.3	1.2		6.6	5.7	5.9	4.1
Married, %	42.8	48.0	47.7	10.6		42.4	44.2	43.7	3.6
Any service-connected disability, %	31.9	30.9	30.9	2.3		32.1	32.7	32.6	1.2
Required copayment, %	12.1	10.1	10.2	6.5		12.0	12.5	12.3	1.4
VAMC Census Region, %									
Northeast	14.9	13.5	13.6	3.9		14.8	14.8	14.8	0.1
Midwest	20.9	23.5	23.4	6.5		21.0	21.2	21.2	0.6
South	44.9	42.3	42.5	5.2		44.8	45.2	45.1	1.0
West	18.3	19.1	19.0	1.9		18.4	18.3	18.3	0.4
Outside Census Regions	1.1	1.6	1.5	4.3		1.1	0.5	0.6	7.1
Fiscal year of index admission, mean (SD)	2005.3 (1.4)	2005.3 (1.4)	2005.3 (1.4)	1.6		2005.3 (1.4)	2005.3 (1.4)	2005.3 (1.4)	0.3
Length of Stay, index hospitalization, days, mean (SD)	5.9 (5.4)	5.8 (6.0)	5.8 (6.0)	1.9		6.0 (5.4)	6.3 (6.3)	6.2 (6.1)	6.2
Long-term care admissions, %	14.5	15.3	15.2	2.2		14.6	15.3	15.1	2.2
Use of non-VA outpatient services, % [e]	20.9	26.8	26.4	13.9		20.8	24.2	23.3	8.3

Potential contraindications to CCBs, %[e]		14.7	23.0	22.5	21.3		14.8	15.0	14.9	0.5
History of stroke or transient ischemic attack, %		16.0	15.3	15.3	1.9		15.6	17.1	16.7	3.9
History of cardiovascular disease, %										
	HF hospitalization	22.3	30.1	29.7	17.6		22.5	23.0	22.9	1.3
	Coronary artery disease	70.6	84.7	84.0	34.3		71.1	73.2	72.6	4.7
	AMI	29.8	49.1	48.1	40.3		30.0	32.3	31.7	5.1
	Angina	19.2	24.5	24.2	12.9		19.3	20.6	20.3	3.4
	Percutaneous Intervention	3.0	7.3	7.1	19.7		3.0	3.8	3.6	4.3
	CABG	1.1	2.6	2.5	11.6		1.1	1.4	1.3	2.6
	Pacemaker/defibrillator, %	12.1	33.5	32.4	52.7		12.2	12.2	12.2	0.1
Concomitant heart failure therapy, %										
	Angiotensin-converting enzyme inhibitors	74.0	67.2	67.5	15.1		73.9	73.3	73.5	1.2
	Angiotensin receptor blockers	5.3	7.6	7.5	9.4		5.4	5.7	5.6	1.7
	Anti-arrhythmic drugs	5.1	10.2	9.9	19.1		5.1	5.5	5.4	1.7
	Anticoagulants	70.0	56.2	56.9	29.0		69.8	69.3	69.4	1.2
	Aspirin	45.3	47.9	47.7	5.1		45.2	45.9	45.7	1.5
	β-blockers	60.6	72.7	72.1	25.8		60.8	61.9	61.6	2.1
	Digoxin	53.2	42.3	42.9	21.9		52.9	50.8	51.4	4.1
	Loop diuretics	86.2	81.3	81.5	13.3		86.1	85.4	85.5	2.1
	Potassium-sparing diuretics	18.5	26.5	26.1	19.3		18.4	18.5	18.5	0.2
	Other diuretics	6.6	7.5	7.5	3.6		6.2	6.3	6.3	0.2
	Hydralazine	5.7	7.1	7.0	5.5		5.8	5.5	5.6	1.2
	Nitrates	25.3	31.8	31.4	14.4		25.3	26.0	25.8	1.6
Laboratory Values, mean (SD)										
	Hematocrit, %	38.4 (5.5)	37.4 (5.6)	37.5 (5.6)	17.4		38.4 (5.5)	38.2 (5.6)	38.2 (5.6)	3.3
	Mean blood pressure, mmHg	96.3 (16.3)	91.0 (15.6)	91.3 (15.7)	2.4		96.2 (16.2)	95.4 (16.6)	95.6 (16.5)	0.2
	Systolic blood pressure, mmHg	132.2 (22.9)	126.5 (22.3)	126.8 (22.4)	10.3		132.0 (22.9)	131.6 (23.4)	131.7 (23.2)	2.4
	Diastolic blood pressure, mmHg	78.4 (15.8)	73.3 (14.9)	73.6 (15)	33.0		78.3 (15.7)	77.3 (15.8)	77.6 (15.8)	4.9
	Pulse, beats/minute	93.7 (23.1)	81.8 (19)	82.4 (19.4)	24.9		93.4 (22.9)	91.4 (22.6)	91.9 (22.7)	1.7

	Serum creatinine, mg/dL	1.4 (0.6)	1.5 (0.7)	1.5 (0.7)	33.1		1.4 (0.6)	1.4 (0.6)	1.4 (0.6)	6.3
	Blood urea nitrogen, mg/dL	26.6 (13.1)	30.1 (16.5)	29.9 (16.3)	56.2		26.6 (13.1)	27 (14.2)	26.9 (13.9)	8.7
	eGFR, ml/min/1.73m²	59.6 (20.9)	55.3 (20.8)	55.5 (20.9)	15.9		59.6 (20.9)	58.3 (20.6)	58.6 (20.7)	3.4
	Sodium, mEq/L	138.1 (3.9)	138.0 (3.9)	138.0 (3.9)	23.5		138 (3.9)	138.0 (4.0)	138.0 (4.0)	3.0
	Potassium, mEq/L	3.9 (0.5)	4.0 (0.5)	4.0 (0.5)	21.0		3.9 (0.5)	4.0 (0.5)	4.0 (0.5)	6.1
	BMI, kg/m²	30.4 (7.7)	29.1 (6.7)	29.2 (6.8)	17.0		30.3 (7.7)	30.4 (7.5)	30.4 (7.5)	0.8
Number of comorbid conditions, mean (SD)[c]		4.8 (2.2)	5.0 (2.3)	5.0 (2.3)	9.6		4.8 (2.2)	4.9 (2.3)	4.9 (2.3)	2.8
Comorbid conditions, %[c]										
	Valvular disease	28.1	34.8	34.4	14.5		28.1	30.0	29.5	4.3
	Pulmonary circulation disorders	17.5	14.9	15.0	6.9		17.6	16.4	16.7	3.1
	Peripheral vascular disease	23.2	26.5	26.3	7.5		23.1	24.6	24.2	3.5
	Hypertension	89.8	88.9	89.0	2.8		89.9	89.2	89.4	2.4
	Paralysis	5.7	4.8	4.9	4.2		5.6	6.3	6.1	3.3
	Other neurological	9.2	7.6	7.6	5.8		9.0	8.8	8.9	0.5
	Chronic pulmonary disease	58.7	49.9	50.4	17.8		58.7	60.0	59.6	2.6
	Diabetes (uncomplicated)	25.1	27.0	26.9	4.2		25.3	24.6	24.7	1.7
	Diabetes (complicated)	17.0	23.3	22.9	15.6		17.1	19.5	18.9	6.1
	Hypothyroidism	10.9	14.2	14.1	10.2		10.7	11.4	11.2	2.2
	Renal failure	17.0	24.2	23.9	17.9		16.9	19.3	18.7	6.1
	Liver disease	4.0	5.1	5.0	5.0		4.1	4.1	4.1	0.1
	Peptic ulcer disease	0.4	0.4	0.4	0.8		0.4	0.4	0.4	0.8
	AIDS/HIV	0.4	0.3	0.3	2.7		0.4	0.5	0.5	0.4
	Lymphoma	1.1	1.2	1.2	0.8		1.1	1.3	1.2	2.0
	Metastatic cancer	1.7	1.2	1.2	4.2		1.7	2.1	2.0	2.9
	Solid tumor without metastasis	8.7	12.9	12.6	13.4		8.8	7.6	7.9	4.2
	Rheumatoid arthritis/collagen vascular diseases	3.4	2.8	2.8	3.7		3.4	3.5	3.5	0.3
	Coagulopathy	11.1	16.3	16.0	15.3		11.1	12.0	11.8	2.7
	Obesity	22.8	18.6	18.8	10.4		22.3	21.0	21.3	3.1
	Weight loss	7.7	8.2	8.2	2.1		7.7	7.6	7.7	0.3
	Fluid and electrolyte disorders	37.2	38.3	38.3	2.2		37.3	37.3	37.3	0.1

	Blood loss anemia	1.5	3.1	3.0	10.7		1.5	2.2	2.0	5.1
	Deficiency anemias	27.7	37.9	37.4	22.0		27.8	29.0	28.7	2.6
	Alcohol abuse	14.0	9.7	10.0	13.3		14.1	12.6	13.0	4.5
	Drug abuse	6.6	3.7	3.9	13.1		6.6	5.7	5.9	4.1
	Psychoses	11.1	8.9	9.1	7.1		11.1	11.9	11.7	2.3
	Depression	20.4	19.0	19.0	3.7		20.3	19.3	19.5	2.7

Abbreviations: DHP= dihydropyridine; CCB= calcium channel blocker; HF = heart failure; CABG = coronary artery bypass grafting; AMI = acute myocardial infarction; eGFR = estimated glomerular filtration rate; VAMC = Veterans Affairs Medical Center; SD= standard deviation

a Absolute standardized difference (percentile) in covariate means and proportions

[b] Race values do not add up to 100% due to unknown race (<1%)

[c] Comorbid conditions include a total of 28 Elixhauser comorbid conditions

[d] Potential contraindications to CCBs include: advanced atrioventricular block without a pacemaker, sick sinus syndrome without a pacemaker, hypotension, or systolic blood pressure < 85 mmHg at index admission

[e] Use of non-VA services = at least one Medicare outpatient visit in the year following the patient's index date

Table 3-2. Results of Sensitivity Analyses Including 349 Patients who Received a Non-Dihydropyridine Calcium Channel blocker Prior to Admission but not at Discharge

	Primary Analysis (n=1,791)		Model 1[a] (n=1,450)		Model 2[b] (n=3,113)	
Outcome	HR (95% CI)	Log-rank P	HR (95% CI)	Log-rank P	HR (95% CI)	Log-rank P
All-cause mortality	0.73 (0.55, 0.96)	0.04	0.86 (0.63, 1.17)	0.22	0.80 (0.65, 0.98)	0.03
Heart failure re-hospitalization	0.95 (0.79, 1.15)	0.42	1.08 (0.88, 1.33)	0.93	0.96 (0.84, 1.10)	0.55

Abbreviations: DHP=dihydropyridine; HR=hazard ratio; CI=confidence interval
[a]Model 1 included potentially misclassified patients among patients who did not receive a calcium channel blocker at discharge
[b]Model 2 added potentially misclassified patients to those who received a non-DHP calcium channel blocker at discharge

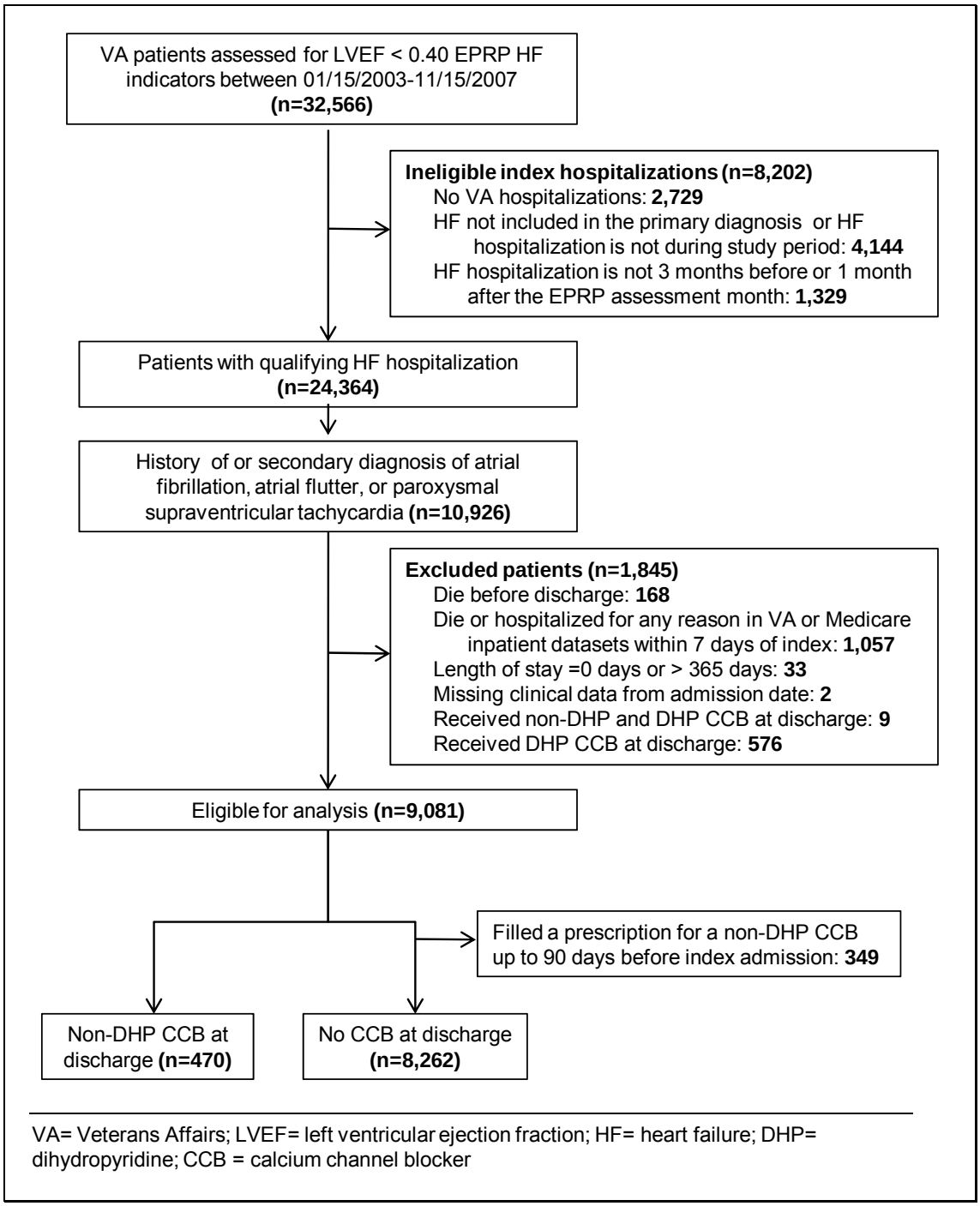

Figure 3-1. Selection of Study Cohort

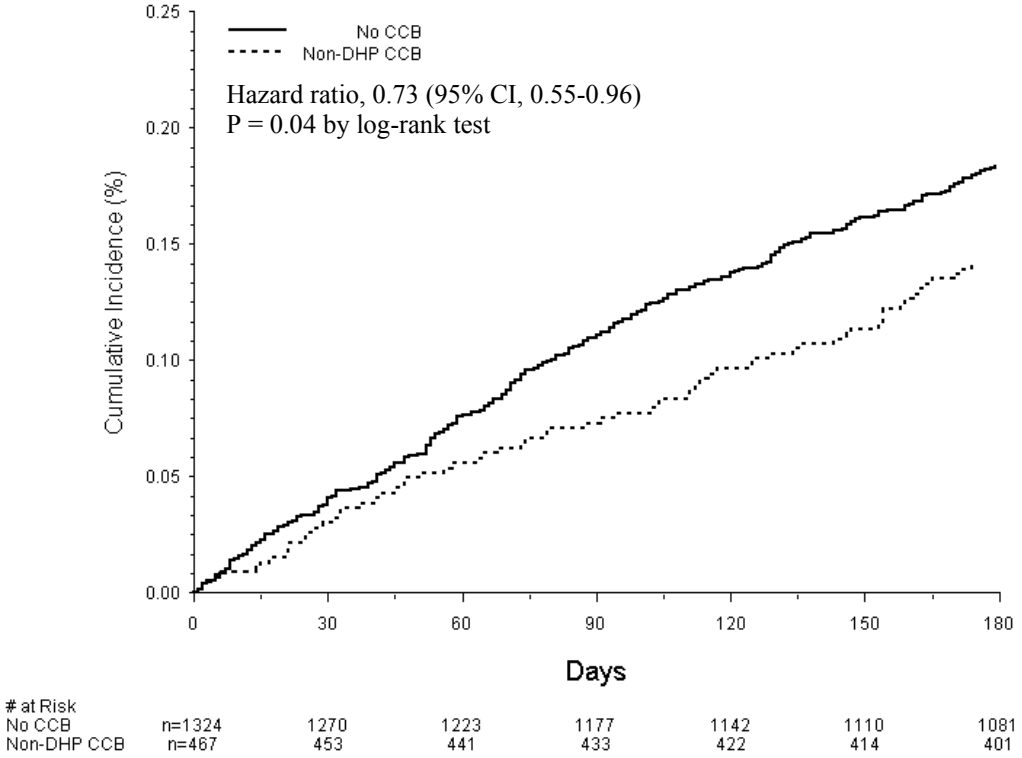

Figure 3-2. Kaplan-Meier Curves for the Probability of All-Cause Mortality According to Receipt of a Non-Dihydropyridine Calcium Blocker at Discharge

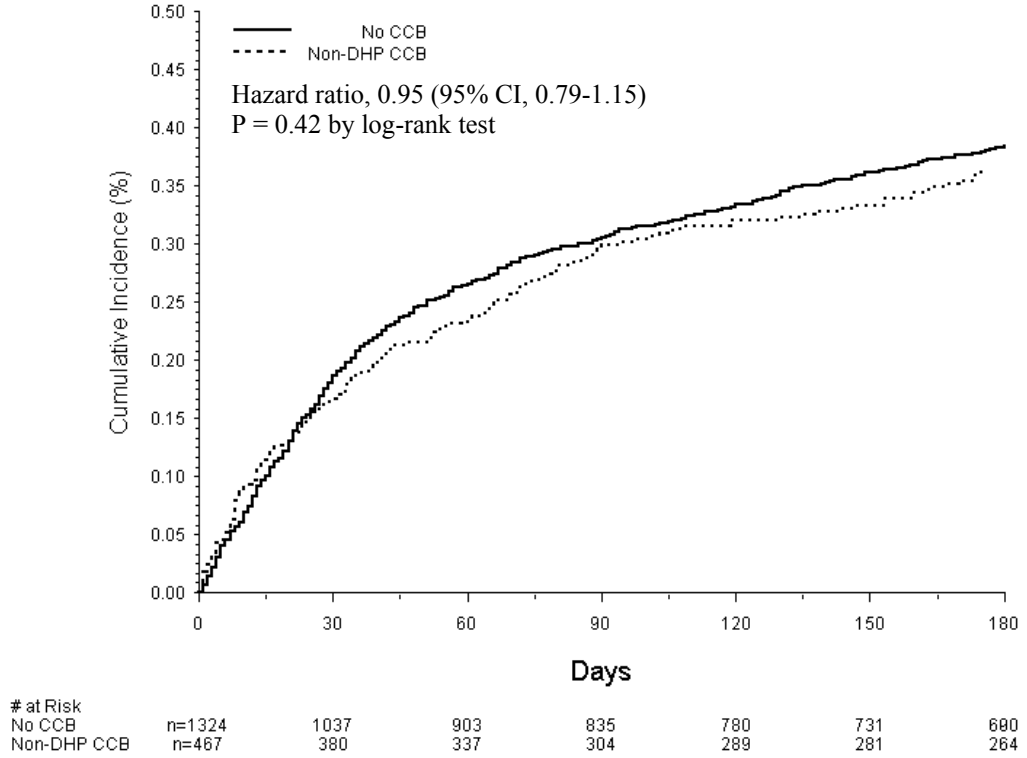

Figure 3-3. Kaplan-Meier Curves for the Probability of Rehospitalization for Heart Failure According to Receipt of a Non-Dihydropyridine Calcium Blocker at Discharge

CHAPTER 4 :
FUTURE DIRECTIONS

In conclusion, we observed hospitalized HF patients and those with comorbid conditions were less likely to receive optimal HF therapies at discharge. In our first study, we studied patients who, based on their baseline characteristics, were eligible to receive any of the 3 therapy options at discharge. Only 61% of patients from the original sample received guideline-recommended, combined ACEI/ARB and BB therapy at hospital discharge, even though patients receiving this treatment option had the lowest occurrence of events during follow-up.

Over half of patients in our second study had comorbid renal dysfunction, an exclusion criterion in clinical trials of HF therapies. We observed that the proportion of patients who received an ACEI or ARB at discharge fell in conjunction with severity of renal function. However, we found that even among patients with the lowest level of renal function studied, there was a significant reduction in rehospitalization for HF after one year. The underuse of ACEI/ARB therapy among patients with HF with LVSD and renal dysfunction, therefore, deprives patients of a potentially beneficial discharge therapy.

In our third study, we examined a therapy uncommonly used among HF patients with LVSD because of safety concerns despite the potential benefit of non-DHP CCB therapy among patients with atrial arrhythmias (42% of our original sample). The risk in mortality associated with non-DHP CCBs in HF patients with LVSD was observed in a

single multicenter trial where half of patients received concomitant BB therapy and there was no report of treatment with renin-angiotensin inhibitors. In more recent studies among HF patients receiving renin-angiotensin inhibitors, non-DHP CCBs had neutral and beneficial associations with cardiac events and mortality. Our study included 470 patients who received a non-DHP CCB at discharge (5% of patients with atrial arrhythmias and HF with LVSD in our study population), and we found non-DHP CCB use was associated with a reduction in mortality within 6 months. In contrast with early examinations of this research question, the majority of patients in our study received concomitant renin-angiotensin inhibitor and BB therapy at discharge.

Although we identified treatment options associated with better patient outcomes in each study, a number of questions remain and lays the framework for future research. In study one, we did not examine the dose of BB a patient received at discharge. Our findings related to individual BB therapy users could be related to dosing of BBs below clinically-beneficial levels because of concerns about adverse effects in decompensated HF patients. We also observed that a number of patients with similar measured baseline characteristics received different individual therapies. It is possible, therefore, that some of the differences in study outcomes between patients in these treatment groups is due to variation in prescribing between VA medical centers. However, because only had information on a random sample of HF patients from each VA, we were unable to address this question. Based on the findings of our second study, it would be useful to examine whether the beneficial treatment effect of ACEI/ARB therapy we observed varied between existing ACEI/ARB users and those initiated on this therapy during their index admission. Lastly, given the known synergy between renin-angiotensin system

inhibitors and calcium channel blockers in the treatment of other cardiovascular diseases, the comparative effectiveness of non-DHP CCBs and renin-angiotensin system inhibitors should be evaluated against other antiarrhythmic pharmacotherapies among HF patients with LVSD and cardiac arrhythmias, as management of arrhythmias can improve HF-related outcomes.

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