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Effects of ACE Inhibitors in Systolic Heart Failure Patients with Chronic Kidney Disease:

A Propensity Score Analysis

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Abstract

Background—Chronic kidney disease (CKD) is common in systolic heart failure (SHF) and is associated with poor outcomes. It is also associated with underuse of angiotensin-converting enzyme inhibitors (ACEI), yet the effect of these drugs in these (SHF-CKD) patients has not been well studied. The objective of this analysis was to determine if ACEI use was associated with reduction in mortality and hospitalization in SHF-CKD patients.

Methods and Results—Of the 6,800 SHF patients (ejection fraction ≤45%) in the Digitalis Investigation Group trial, 1,707 had CKD (serum creatinine 1.3-2.5 mg/dl for women and 1.5-2.5 mg/dl for men). Propensity scores for ACE inhibitor use were calculated for each of the 1,707 patients and were used to match 104 of the 127 no-ACEI patients with 104 ACEI patients. We estimated the effect of ACEI use on outcomes at 2 years using multivariable-adjusted Cox regression analyses. Overall, 35% died and 67% were hospitalized. Compared with 30% ACEI patients, 39% no-ACEI patients died (adjusted HR=0.58; 95% CI=0.35-0.96; p=0.034). Compared with 64% ACEI patients, 69% no-ACEI patients had hospitalizations due to all causes (adjusted HR=0.69; 95% CI=0.48-0.98; p=0.040).

Conclusion—We observed an association between use of ACEI and reductions in mortality and hospitalization in ambulatory chronic SHF patients with mild to moderate CKD. However, the results of this observational study should be interpreted with caution, and need to be replicated in larger and more recent databases, and confirmed prospectively in well-designed follow-up studies and/or randomized clinical trials.

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Keywords

heart failure; chronic kidney disease; ACE inhibitors; mortality; hospitalization

Angiotensin-converting enzyme (ACE) inhibitors reduce mortality and morbidity in patients with systolic heart failure (SHF or clinical heart failure with impaired left ventricular ejection fraction.[1, 2] It is also associated with renoprotection and reduction in mortality in patients with chronic kidney disease (CKD).[3-5] Despite a theoretical dual benefit from the use of ACE inhibitors in SHF patients with CKD, these drugs are often underused in these patients.[6-8] This is particularly important as CKD is common in SHF and is associated with poor outcomes.[8, 9]

ACE inhibitors has been shown to be associated with reduction in short- and long-term mortality in hospitalized older adults with acute systolic HF and advanced CKD.[8, 10] However, the benefit of ACE inhibitors in ambulatory systolic HF patients with mild to moderate CKD has not been well studied.[11] In this analysis, we tested the hypothesis that ACE inhibitor use was associated with reduction in mortality and hospitalization in propensity score matched cohort of ambulatory chronic SHF patients with mild to moderate CKD.

Methods

Data source

Using standard protocols, we obtained the DIG dataset from the National Heart, Lung and Blood Institute of the National Institutes of Health. The University of Alabama at Birmingham approved an application for expedited review for the current study.

Patients

The randomized DIG trial, conducted during 1991-1993 in the United States (186 centers) and Canada (116 centers) enrolled 6,800 ambulatory patients with chronic SHF and normal sinus rhythm.[12, 13] The objective of the trial was to evaluate the effects of digoxin on mortality and hospitalizations in HF. The DIG protocol encouraged the use of ACE inhibitors in all participants in the absence of specific contraindications or prior intolerance, and over 94% of patients were receiving ACE inhibitors at the time of randomization. Of the 6,800 patients with systolic HF, 1,707 had CKD as define below.

Chronic Kidney Disease

We defined CKD as baseline serum creatinine of 1.5 mg/dl or higher for men and 1.3 mg/dl or higher for women. Patients with serum creatinine 2.5 mg/dl or higher were not enrolled in the DIG trial. We chose to use serum creatinine over estimated glomerular filtration rate (GFR) [14] for several reasons. First, in ambulatory care settings most clinicians use serum creatinine, rather than an estimated GFR, to evaluate kidney function. Second, estimated GFR is an unreliable tool to identify CKD in patients in otherwise good health and without CKD.[15] Finally, serum creatinine of 1.5 mg/dl or higher for men and 1.3 mg/dl or higher for women has often been used to define CKD in the literature.[16-18] In contrast to early stages of CKD, serum creatinine is a more reliable marker of CKD in the later stages.[19] Patients included in our analysis had a median estimated GFR of 42 ml/min/1.73 m^2.

Outcomes

The primary outcome of the DIG study was all-cause mortality with a mean follow up of 37 months (range 28 to 58 months). All-cause mortality was also the primary outcome of this study, but because few events occurred after the second year, especially in patients not receiving

ACE inhibitors (number at risk at 3 and 4 years were 41 and 14, respectively), we restricted our analysis to two-year mortality. We also examined the effect of ACE inhibitor use on 2-year all-cause hospitalization.

Statistical analysis

Propensity Score Analysis—Because patients in the DIG trial were not randomly assigned to receive ACE inhibitor therapy, we used propensity scores to control for selection bias[20-24] The propensity score represents the conditional probability of receiving an exposure or therapy given a vector of covariates and is used to adjust for selection bias in observational studies through matching, stratification or direct adjustment.[10, 25-27]

Estimation of Propensity Score—At first, we compared baseline characteristics of 1,707 patients with SHF and CKD receiving and not receiving ACE inhibitors using Pearson Chi-square tests and Student's t tests appropriate. We then estimated the propensity scores or probability for the receipt of an ACE inhibitor for each of the 1,707 patients using a non-parsimonious multivariable logistic regression model.[21, 28] Covariates in the model included age, sex, race, body mass index, duration of HF, etiology of HF (ischemic, hypertensive, idiopathic, and other), prior myocardial infarction, current angina, hypertension, diabetes, diuretic, potassium-sparing diuretics, combined use of nitroglycerin and hydralazine, pre-trial use of digoxin, limitation in physical activities, New York Heart Association (NYHA) functional class, dyspnea at rest, dyspnea on exertion, third heart sound, elevated jugular venous pressure, pulmonary râles, lower extremity edema, pulmonary congestion, cardiothoracic ratio >0.5, serum creatinine and potassium levels, echocardiographic estimation of left ventricular ejection fraction, and the interaction of age and serum creatinine. This set of covariates was designed to incorporate assessments of all key elements of the ACE inhibitor treatment decision. The model calibrated (Hosmer-Lemeshow test: $p = 0.630$) and discriminated (area under the ROC curve; $C = 0.77$) well.

Propensity Score Matching—Propensity score matching allows us to balance the distributions of all baseline characteristics incorporated in our propensity model. Unlike randomized controlled trials in which both measured and unmeasured covariates are expected to be similarly distributed across treatment groups, in propensity matching of observational studies, one can achieve a balanced distribution only of the measured covariates. Therefore, a key assumption in studies using propensity matching is that "hidden" or unmeasured covariates are sufficiently balanced across the matched treatment and control groups so as to not bias our conclusions[29] While this assumption cannot be tested directly, we can assess the robustness of our conclusions with sensitivity analyses.

We used a SPSS macro to match patients according to their estimated propensity for receipt of ACE inhibitors.[30] In our matching algorithm, we first matched each patient not receiving an ACE inhibitor with another patient receiving ACE inhibitor who had the same 5-digit propensity score. Matched patients were then removed from the file and the above process was then repeated on the remaining file, each time matching by 4-, 3-, 2-, and 1-digit propensity scores. In all, 104 of the 127 patients not receiving ACE inhibitors were matched with 104 patients receiving ACE inhibitors.

Effectiveness of Propensity Score Matching—Before matching (n=1,707), the mean (95% confidence interval) propensity score for patients receiving ACE inhibitors was 0.93990 (0.93635 - 94344) and that for patients not receiving ACE inhibitors was 0.74774 (0.69778 - 0.79769) ($p < 0.0001$). After matching (n=208), the mean propensity score for patients receiving ACE inhibitors was 0.85142 (0.81611 - 88673) and that for those not receiving ACE inhibitors was 0.85121 (0.81571 - 88671) ($p=0.993$). Table 1 provides details on the balance of these

characteristics across the ACE inhibitor and non-ACE inhibitor groups before and after propensity score matching.

To determine if the propensity score matching produced balanced distributions of baseline characteristics across the non-ACE inhibitor and ACE inhibitor groups, we measured covariate imbalance using standardized differences, which describe the observable selection bias remaining after matching. The standardized difference is the difference of the group means (or proportions, in the case of binary covariates) expressed as a percentage of an appropriate (pooled) standard deviation.[25, 27] A perfectly balanced covariate will have a standardized difference of 0%. Standardized differences substantially exceeding 10% in absolute value after matching suggest relatively poor balance,[25] and indicate the need for additional covariate adjustments (i.e. through regression) in order to develop fair assessments of the treatment effect.

Survival Analysis—After assessing the adequacy of our propensity match, we constructed survival curves to describe the 208 matched patients by receipt of ACE inhibitors using Kaplan-Meier estimates and assessed statistical significance based on the log-rank test. In plotting the survival curves, we first estimated mean 2-year unadjusted survival times for patients stratified by receipt or non-receipt of ACE inhibitors. The association of ACE inhibitor therapy with all-cause, 2-year mortality was determined using bivariate Cox proportional hazard regression analyses. We then used a multivariable Cox proportional hazard model to determine the risk of 2-year mortality adjusted by propensity scores and other covariates. The covariates in the model included those used in the propensity score model. Use of digoxin during the trial was also included in the model. Age, sex, race, and key covariates with >10% post-match standardized differences, namely, body mass index, duration of HF, current angina, hypertension, diabetes, use of potassium supplement, dyspnea at rest, elevated jugular venous pressure, pulmonary râles, edema, and NYHA class III-IV were forced into the model. All other covariates were entered in a forward stepwise fashion. A similar approach was use to examine the effect of ACE inhibitors on 2-year all-cause hospitalizations. We also repeated our analysis in the pre-match cohort of patients using a similar approach. All statistical tests were evaluated using a two-tailed 95% confidence level. Analyses were performed using SPSS for Windows (Release 13).[31]

Results

Patient characteristics

The mean (±SD) age of the 208 propensity matched patients with SHF and CKD was 68.4 (±9.8) years. Forty two (20.2%) were female and 37 (17.8%) were non-white. Table 1 compares baseline characteristics of 208 propensity score matched patients with CKD by the receipt of ACE inhibitor. Matching reduced the standardized differences for almost all prognostically important variables below 10% in absolute value, including age, sex, race, serum creatinine, and left ventricular ejection fraction. Post-match standardized differences for a few covariates, including diabetes, dyspnea at rest, elevated jugular venous pressure, and NYHA class, exceeded 10% in absolute value, indicating relatively weak balance, and prompting subsequent additional adjustments for these covariates in our Cox regression models.

ACE Inhibitor Use and All-Cause Mortality

Overall, 72 patients (34.6%) died from all causes during a 2-year follow up. Compared with 31 (29.8%) deaths in patients receiving ACE inhibitors, 41 (39.4%) of those not receiving ACE inhibitors died (9.6% absolute risk reduction; Chi-square p =0.145). Figure 1 displays Kaplan-Meier plots for unadjusted 2-year cumulative mortality for patients receiving versus not receiving ACE inhibitor therapy. Unadjusted mean survival was 45 days longer for patients

receiving ACE inhibitors: 613 (95% confidence interval 572 to 655) days for versus 568 (95% confidence interval 523 to 614) days for those not receiving ACE inhibitors (log rank test p = 0.136).

Table 2 demonstrates that among propensity matched patients, ACE inhibitor use was associated with a non-significant 30% relative reduction in the risk of unadjusted all-cause mortality (unadjusted hazard ratio, 0.70; 95% confidence interval, 0.44 to 1.12). Adjustment for covariates made the association stronger and statistically significant (adjusted hazard ratio, 0.59; 95% confidence interval, 0.36 to 0.97). The relationship remained essentially unchanged after additional adjustment for propensity scores. When we examined the effect of ACE inhibitors on mortality for the entire follow up (34 months median), use of ACE inhibitor was associated with a 23% non-significant reduction in mortality (adjusted hazard ratio, 0.77; 95% confidence interval, 0.50 to 1.18). Among the 1,707 pre-match patients, use of ACE inhibitor was associated with a significant 31% relative reduction in all-cause mortality (unadjusted hazard ratio, 0.69; 95% confidence interval, 0.51 to 0.92). The association became weaker and lost significance after adjustment for propensity score; however, remained essentially unchanged after adjustment for covariates.

ACE Inhibitor Use and All-Cause Hospitalization

Overall, 139 (66.8%) patients were hospitalized from all causes during the 2-year follow up. Compared with 64.4% (67 / 104) of patients hospitalized among those receiving ACE inhibitors, 69.2% (41 / 104) of those not receiving ACE inhibitors were hospitalized (4.5% absolute reduction; Chi-square p =0.462). Figure 2 displays Kaplan-Meier plots for unadjusted 2-year cumulative all-cause hospitalization for patients receiving versus not receiving ACE inhibitors. Cumulative survival free from hospitalization for patients receiving ACE inhibitors was 33% (versus 26% for those not receiving these drugs). This represents 54 additional mean days free from hospitalization for patients receiving ACE inhibitors: 401 (95% confidence interval 343 to 459) days versus 347 (95% confidence interval 291 to 403) days for those not receiving ACE inhibitors (log rank test p = 0.136).

Table 3 demonstrates that among propensity matched patients, ACE inhibitor use was associated with a non-significant 18% relative reduction in the risk of unadjusted all-cause hospitalization (unadjusted hazard ratio, 0.82; 95% confidence interval, 0.59 to 1.14). Adjustment for covariates made the association stronger (adjusted hazard ratio, 0.70; 95% confidence interval, 0.49 to 1.01, p=0.054). After further adjustment for propensity score, the relationship remained essentially unchanged (adjusted hazard ratio 0.69; 95% confidence interval 0.48-0.98, p=0.04). Among the 1,707 pre-match patients, use of ACE inhibitor was associated with a significant 26% relative reduction in all-cause hospitalization (unadjusted hazard ratio, 0.74; 95% confidence interval, 0.60 to 0.92). The association became weaker and lost significance after adjustment for propensity score; however, remained essentially unchanged after adjustment for covariates.

Discussion

In ambulatory chronic SHF patients with mild to moderate CKD, ACE inhibitor use was associated with significant reduction in risk-adjusted all-cause mortality and all-cause hospitalizations. These results are important as CKD is common in HF, is associated with poor prognosis,[32] and underuse of ACE inhibitors.[6, 7, 33] However, our data indicate that such an approach is likely to be detrimental.

Comparison with other published studies

We noted a 9.6% reduction in absolute risk of all-cause mortality associated with ACE inhibitor use. This compares favorably with the 4.5% absolute reduction in all-cause death in SHF patients in the SOLVD trial (39.7% deaths in patients receiving placebo versus 35.2% for those receiving enalapril).[34] Compared to the SOLVD trial, patients in our analysis were older (mean age 68 years versus 61 years in SOLVD) and sicker (46% had NYHA class III-IV versus 33% in SOLVD). In addition, they had higher mean serum creatinine (1.8 mg/dL versus 1.2 mg/dL in SOLVD). Treatment effects are often known to depend on severity or stage of the disease, or other comorbidities.[35] In an elderly (mean age 79 years) cohort of hospitalized acute SHF patients with advanced CKD (mean serum creatinine 2.9 mg/dL), use of ACE inhibitor was associated with a 31% absolute reduction in mortality.[8] Therefore, the findings of our study are consistent with other published reports, and are mechanistically plausible. SHF patients with CKD comprise a high-risk segment of the SHF population, and ACE inhibitors likely confer added benefit to these patients through their dual renoprotective and cardioprotective properties.

Clinical Implications

National HF guidelines and manufacturers' package inserts of commonly used ACE inhibitors do not identify CKD as a contraindication to ACE inhibitor use.[1, 8, 36] However, due to the paucity of outcomes data in this population, coupled with concerns about an increased risk for worsening renal function and hyperkalemia,[37, 38] the guidelines alert clinicians to be cautious when using ACE inhibitors in patients with significant CKD[1, 36] Short- and long-term survival benefits of ACE inhibitors in hospitalized older adults with acute SHF and advanced CKD have been documented in the literature.[8, 10] Our analysis demonstrates that in ambulatory patients with chronic mild to moderate SHF and mild to moderate CKD, ACE inhibitor use was associated with reduced mortality and hospitalization. Because there are no randomized clinical trials of ACE inhibitors in SHF patients with CKD, analyses of existing databases using methods such as propensity score analysis will likely provide cumulative evidence for use of ACE inhibitors in these patients. However, because these patients may be at risk for hyperkalemia, serum potassium levels should be closely monitored during initiation and titration of ACE inhibitor therapy.

Even though many clinicians interpret a rise in serum creatinine in response to ACE inhibitor therapy as an indicator of renal damage, the renoprotective properties of ACE inhibitors is well documented in the literature.[3-5] In one study, serum creatinine dropped to baseline after ACE inhibitor therapy was discontinued after 6 years suggesting that there was no permanent structural damage to the kidneys.[38] In deed, many nephrologists compare a rise in serum creatinine in response to ACE inhibitor therapy to bradycardia in response to a beta-blockers and consider that a marker of effectiveness of ACE inhibitor therapy.

Strengths and Limitations

A key strength of our study is that we used propensity scores to specify a matched subgroup of patients within a nonrandomized cohort. Propensity score matching, in combination with additional regression-based adjustments, allowed us to substantially reduce the impact of selection bias due to all observed baseline characteristics in Table 1.

Several key limitations must be acknowledged. First, propensity methods do not account for bias due to unmeasured or hidden covariates. The results of our study are sensitive to potential hidden covariates (normal deviate =1.19, two-tailed p value =0.234).[29] However, sensitivity analysis cannot determine if such a hidden covariate existed. If such a hidden covariate existed, it would only explain away our findings if it correlated with both receipt of ACE inhibitor and clinical outcomes, and if it was not strongly correlated with any of the other variables used in

the propensity model. Of note, the sensitivity analysis was based on our propensity-matched "unadjusted" results, and not based on "additional multivariable adjusted" results.

Another potential limitation of our study is that baseline characteristics were not perfectly balanced in the propensity matched cohorts. This most likely reflects the large number of variables considered for the propensity score analysis and the relatively small number of matched pairs. Nonetheless, it is worth noting that more patients receiving ACE inhibitors had diabetes, dyspnea at rest, elevated jugular venous pressure, and higher NYHA classes (Table 1), which might have increased the risk of adverse events for these patients. When we adjusted for these covariates in the multivariable model, the association between ACE inhibitor use and favorable outcomes became stronger. Exclusion of unmatched patients might be considered a potential limitation. Compared with matched patients receiving ACE inhibitors (n=104), unmatched patients receiving ACE inhibitors (n=1476) had significantly higher propensity to receive these drugs (0.94613 versus 0.85142 for unmatched patients; $p < 0.0001$). As higher propensity or probability of receiving ACE inhibitors might be marker for better outcomes, inclusion of unmatched patients in our analysis would have inflated our findings. Therefore, while exclusion of unmatched patients might have compromised to some degree the generalizability of our findings, it has added internal validity to our results.

Patients with a serum creatinine level of 2.5 mg or higher and atrial fibrillation were excluded from the DIG trial. In addition, DIG participants tended to be younger than most HF patients treated in clinical practice, and women and minorities were under-represented. Studies are also needed to assess the safety and efficacy of ACE inhibitors in patients with HF and preserved left ventricular systolic function.

Conclusions

In ambulatory patients with chronic systolic mild to moderate HF and mild to moderate CKD, use of ACE inhibitors was associated with significant reductions in risk-adjusted all-cause mortality and all-cause hospitalization. The results of this study, based on observational data, are mechanistically plausible and consistent with previous reports. Therefore, these hypothesis-generating finding also provide interim evidence of potential benefits of ACE inhibitors in SHF patients with CKD. However, life-saving therapy with ACE inhibitors is probably being withheld on the basis of questionable evidence. These cumulative evidence of the beneficial effects of ACE inhibitors in SHF patients with CKD calls for a randomized clinical trial of ACE inhibitors in these patients.

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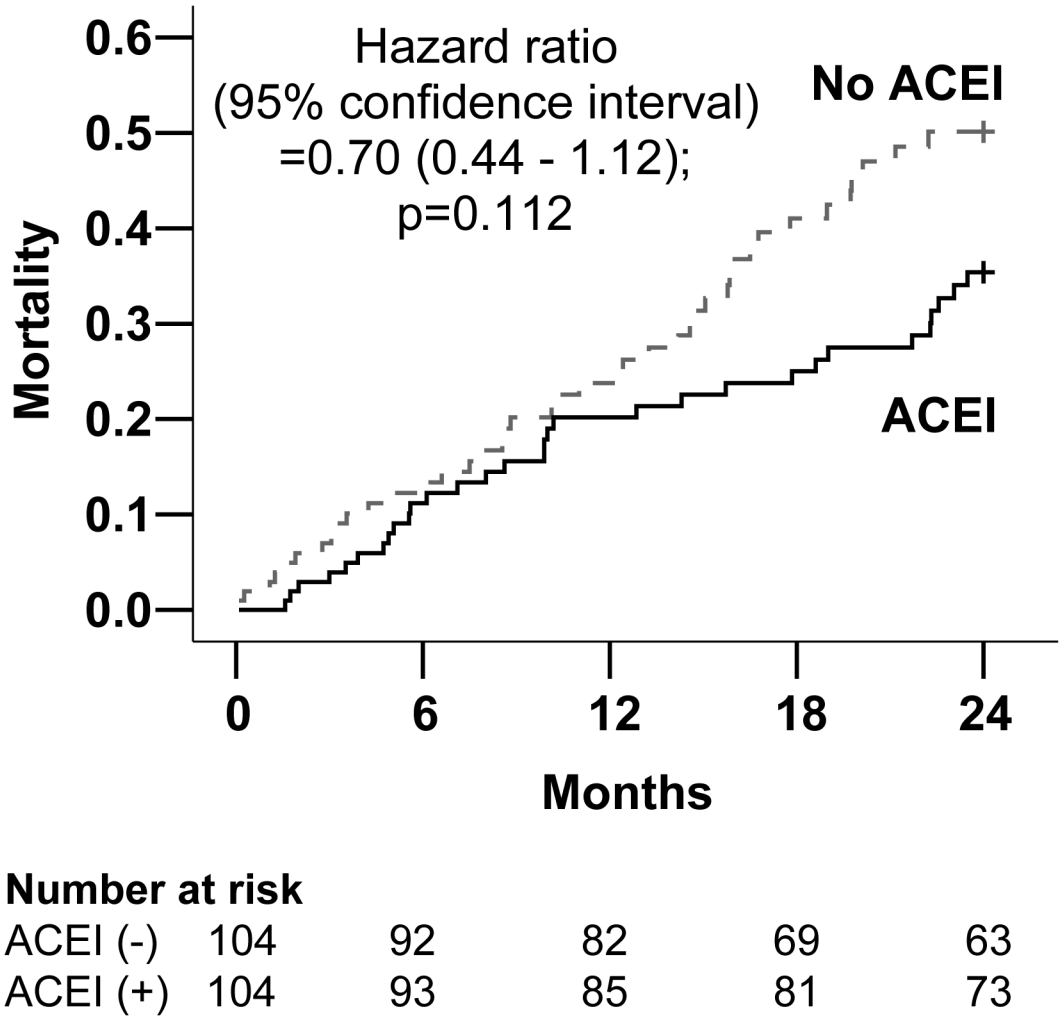
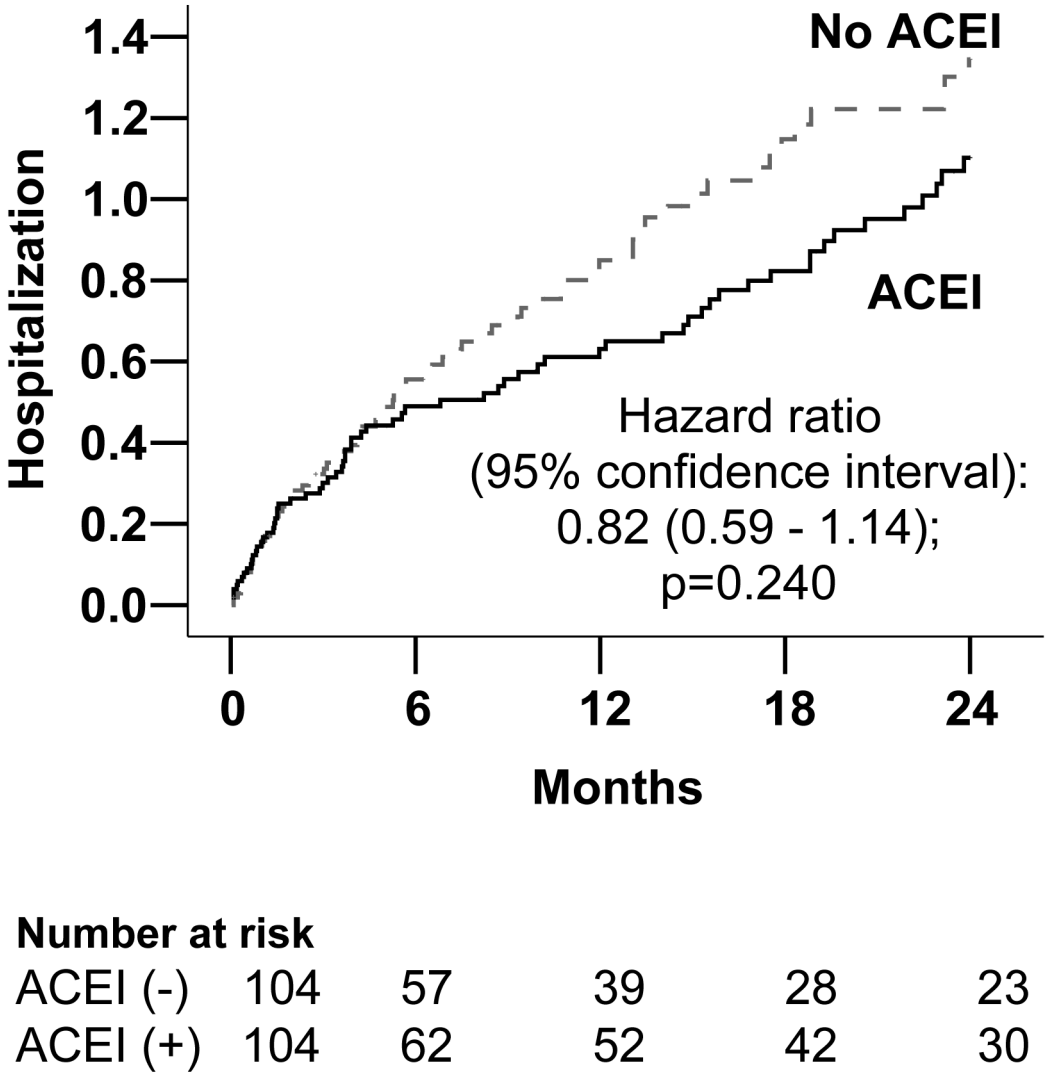


Number at risk

ACEI (-)	104	92	82	69	63
ACEI (+)	104	93	85	81	73

Figure 1.
Kaplan-Meier plots for all-cause mortality



Number at risk

ACEI (-)	104	57	39	28	23
ACEI (+)	104	62	52	42	30

Figure 2.
Kaplan-Meier plots for all-cause hospitalization

Table 1

Baseline patient characteristics by angiotensin-converting enzyme (ACE) inhibitor use before and after propensity score matching

	Pre-match			Post-match		
	No ACE Inhibitors	ACE Inhibitors	P value	No ACE Inhibitors	ACE Inhibitors	P value
% or mean (±SD)	N = 127	N = 1580		N = 104	N = 104	
Age (years)	69.2 (±10.2)	68.2 (±9.7)	0.268	68.7 (±10.3)	68.1 (±9.2)	0.625
Women	29 (22.8%)	375 (23.7%)	0.914	23 (22.1%)	19 (18.3%)	0.605
Non-whites	25 (19.7%)	268 (17.0%)	0.463	19 (18.3%)	18 (17.3%)	>0.999
Body mass index (kilogram / m^2)	26.2 (±4.5)	26.7 (±5.1)	0.289	26.4 (±4.5)	27.5 (±5.5)	0.102
Duration of heart failure (months)	28.6 (±30.9)	32.0 (±39.1)	0.413	29.0 (±31.4)	25.3 (±33.0)	0.413
Etiology of heart failure						
Ischemic	95 (74.8%)	1166 (73.8%)		77 (74.0%)	81 (77.9%)	
Hypertensive	9 (7.1%)	155 (9.8%)	0.403	9 (8.7%)	6 (5.8%)	0.811
Idiopathic	14 (11.0%)	190 (12.0%)		12 (11.5%)	10 (9.6%)	
Others	9 (7.1%)	69 (4.4%)		6 (5.8%)	7 (6.7%)	
Comorbid conditions						
Prior myocardial infarction	83 (65.4%)	1067 (67.5%)	0.624	66 (63.5%)	68 (65.4%)	0.885
Current angina pectoris	40 (31.5%)	446 (28.2%)	0.432	30 (28.8%)	35 (33.7%)	0.550
Hypertension	74 (58.3%)	863 (54.6%)	0.459	59 (56.7%)	53 (51.0%)	0.487
Diabetes Mellitus	42 (33.1%)	543 (34.4%)	0.846	33 (31.7%)	47 (45.2%)	0.064
Medications						
Digoxin (pre-trial use)	55 (43.3%)	688 (43.5%)	>0.999	45 (43.3%)	41 (39.4%)	0.673
Digoxin (during trial)	60 (47.2%)	781 (49.4%)	0.646	48 (46.2%)	49 (47.1%)	>0.999
Diuretics	107 (84.3%)	1379 (87.3%)	0.336	86 (82.7%)	88 (84.6%)	0.852
Potassium-sparing diuretics	16 (12.6%)	145 (9.2%)	0.207	12 (11.5%)	14 (13.5%)	0.834
Nitrates and hydralazine	33 (26.0%)	18 (1.1%)	<0.0001	13 (12.5%)	10 (9.6%)	0.659
Potassium supplement	44 (34.6%)	505 (32.0%)	0.554	36 (34.6%)	28 (26.9%)	0.293
Symptoms and signs						
Dyspnea at rest	41 (32.3%)	409 (25.9%)	0.117	32 (30.8%)	38 (36.5%)	0.463
Dyspnea on exertion	100 (78.7%)	1241 (78.5%)	>0.999	84 (80.8%)	85 (81.7%)	>0.999
Activity limitation	103 (81.1%)	1256 (79.5%)	0.732	84 (80.8%)	86 (82.7%)	0.858
Elevated jugular venous pressure	27 (21.3%)	285 (18.0%)	0.403	21 (20.2%)	31 (29.8%)	0.149
Third heart sound	31 (24.4%)	461 (29.2%)	0.308	23 (22.1%)	21 (20.2%)	0.865
Pulmonary râles	40 (31.5%)	317 (20.1%)	0.004	30 (28.8%)	38 (36.5%)	0.301
Leg edema	33 (26.0%)	385 (24.4%)	0.683	23 (22.1%)	29 (27.9%)	0.442
NYHA functional class						
I	13 (10.2%)	156 (9.9%)		12 (11.5%)	9 (8.7%)	
II	58 (45.7%)	781 (49.4%)	0.006	48 (46.2%)	43 (41.3%)	0.634
III	44 (34.6%)	591 (37.4%)		36 (34.6%)	40 (38.5%)	
IV	12 (9.4%)	52 (3.3%)		8 (7.7%)	12 (11.5%)	
Heart rate (per minute)	83.3 (±13.9)	78.6 (±12.8)	<0.0001	83.2 (±14.4)	84.3 (±13.1)	0.576
Blood pressure (mm Hg)						
Systolic	130.5 (±20.8)	127.7 (±21.6)	0.160	129.5 (±20.8)	128.5 (±21.1)	0.725
Diastolic	76.5 (±10.4)	74.3 (±11.8)	0.035	75.5 (±9.9)	76.1 (±12.0)	0.674
Chest x-ray findings						
Pulmonary congestion	26 (20.5%)	295 (18.7%)	0.637	20 (19.2%)	21 (20.2%)	>0.999
Cardiothoracic ratio >0.5	85 (66.9%)	1053 (66.6%)	>0.999	66 (63.5%)	65 (62.5%)	>0.999
Laboratory data						
Serum potassium (mEq/L)	4.4 (±0.48)	4.4 (±0.47)	0.782	4.39 (±0.45)	4.43 (±0.43)	0.616
Serum creatinine (mg/dL),	1.88 (±0.44)	1.76 (±0.34)	<0.0001	1.81 (±0.40)	1.83 (±0.39)	0.757
Estimated GFR (ml/min/1.73 m^2)	39.5 (±10.3)	41.5 (±8.8)	0.014	40.8 (±9.5)	40.6 (±9.3)	0.889
Ejection fraction (%),mean (±SD)	29.2 (±9.0)	28.0 (±8.9)	0.142	28.8 (±9.0)	28.4 (±8.8)	0.708

GFR=glomerular filtration rate, HF=heart failure, JVP=jugular venous pressure, NYHA=New York heart association

Table 2

Crude and adjusted hazard ratios (95% confidence intervals) for 2-year all-cause mortality for ambulatory chronic heart failure patients with systolic dysfunction and chronic kidney disease by use of angiotensin-converting enzyme (ACE) inhibitors

	Hazard ratio (95% confidence interval)	P values
Pre-match (n=1,707)	0.69 (0.51 - 0.92)	0.016
Pre-match: Adjusted for propensity scores	0.83 (0.59 - 1.17)	0.292
Pre-match: Adjusted* for covariates	0.66 (0.49 - 0.90)	0.008
Post-match (n=208)	0.70 (0.44 - 1.12)	0.112
Post-match: Adjusted** for covariates	0.59 (0.36 - 0.97)	0.039
Post-match: Adjusted** for covariates and propensity scores	0.58 (0.35 - 0.96)	0.034

* Covariates in the final model included age, sex, race, diabetes, pulmonary râles, NYHA class III-IV, pre-trial use of digoxin, diastolic blood pressure, serum creatinine, cardiothoracic ration >0.50, and number of symptoms and signs of heart failure.

** Covariates in the final model included age, sex, race, body mass index, duration of heart failure, angina, hypertension, diabetes, use of potassium supplement, dyspnea at rest, elevated jugular venous pressure, pulmonary râles, edema, NYHA class III-IV, diastolic blood pressure, serum creatinine, and number of symptoms and signs of heart failure.

Table 3

Crude and adjusted hazard ratios (95% confidence intervals) for 2-year all-cause hospitalization for ambulatory chronic heart failure patients with systolic dysfunction and chronic kidney disease by use of ACE inhibitors

	Hazard ratio (95% confidence interval)	P values
Pre-match (n=1,707)	0.74 (0.60 - 0.92)	0.007
Pre-match: Adjusted for propensity scores	0.83 (0.65 - 1.06)	0.128
Pre-match: Adjusted* for covariates	0.77 (0.61 - 0.96)	0.019
Post-match (n=208)	0.82 (0.59 - 1.14)	0.240
Post-match: Adjusted** for covariates	0.70 (0.49 - 1.01)	0.054
Post-match: Adjusted** for covariates and propensity scores	0.69 (0.48 - 0.98)	0.040

* Covariates in the final model included age, sex, race, diabetes, pre-trial use of digoxin, use of potassium supplement, dyspnea on exertion, pulmonary râles, edema, NYHA class III-IV, diastolic blood pressure, serum creatinine, and cardiothoracic ratio >0.50.

** Covariates in the final model included age, sex, race, body mass index, duration of heart failure, angina, hypertension, diabetes, use of potassium supplement, dyspnea at rest, elevated jugular venous pressure, pulmonary râles, edema, NYHA class III-IV, diastolic blood pressure, and serum creatinine