Published in final edited form as:
Am J Med. 2013 May ; 126(5): 401–410. doi:10.1016/j.amjmed.2013.01.004.

Angiotensin-Converting Enzyme Inhibitors and Outcomes in Heart Failure and Preserved Ejection Fraction

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Abstract

BACKGROUND—The role of angiotensin-converting enzyme (ACE) inhibitors in patients with heart failure and preserved ejection fraction remains unclear.

METHODS—Of the 10,570 patients ≥65 years with heart failure and preserved ejection fraction (≥40%) in OPTIMIZE-HF (2003–2004) linked to Medicare (through December, 2008), 7304 were not receiving angiotensin receptor blockers and had no contraindications to ACE inhibitors. After excluding 3115 patients with pre-admission ACE inhibitor use, the remaining 4189 were eligible for new discharge prescriptions for ACE inhibitors, and 1706 received them. Propensity scores for the receipt of ACE inhibitors, calculated for each of the 4189 patients, were used to assemble a cohort of 1337 pairs of patients, balanced on 114 baseline characteristics.

RESULTS—Matched patients had a mean age of 81 years, mean ejection fraction of 55%, 64% were women and 9% African American. Initiation of ACE inhibitor therapy was associated with lower risk of the primary composite endpoint of all-cause mortality or heart failure hospitalization during 2.4 years of median follow-up (hazard ratio {HR}, 0.91; 95% confidence interval {CI},

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Conflict of Interest: None

Authorship: AA conceived the study hypothesis and design in collaboration with coauthors. AA and MM wrote the first draft. AA, MM, KP performed statistical analyses in collaboration with IA, TL, and YZ. All authors interpreted the data, participated in critical revision of the paper for important intellectual content, and approved the final version of the article. IA, AA, MM, KP and YZ had full access to the data.

0.84–0.99; p=0.028), but not with individual endpoints of all-cause mortality (HR, 0.96; 95% CI, 0.88–1.05; p=0.373) or heart failure hospitalization (HR, 0.93; 95% CI, 0.83–1.05; p=0.257).

CONCLUSION—In hospitalized older patients with heart failure and preserved ejection fraction not receiving angiotensin receptor blockers, discharge initiation of ACE inhibitor therapy was associated with a modest improvement in the composite endpoint of total mortality or heart failure hospitalization, but had no association with individual endpoint components.

Keywords

ACE inhibitors; Heart Failure; Preserved Ejection Fraction

Nearly half of the estimated 6 million heart failure patients in the United States have diastolic heart failure or heart failure with preserved ejection fraction.[1] Most of these patients are older adults and they are prognostically similar to those with systolic heart failure or heart failure with reduced ejection fraction.[2,3] Angiotensin-converting enzyme (ACE) inhibitors reduce all-cause mortality in patients with heart failure and reduced ejection fraction.[4-6] Although angiotensin receptor blockers did not reduce mortality in patients with heart failure and reduced ejection fraction, they improved outcomes,[7,8] and are considered drugs of choice for these patients who cannot tolerate ACE inhibitors.[9] However, despite evidence of similar neurohormonal activation in heart failure with preserved ejection fraction,[10] there is no clear evidence of efficacy of renin-angiotensin system inhibition in these patients.

The lack of efficacy of angiotensin receptor blockers in patients with heart failure and preserved ejection fraction has now been well established in two large multicenter randomized controlled trials.[11,12] The role of ACE inhibitors, on the other hand, is less clear. In the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial, the only randomized controlled trial of ACE inhibitors in heart failure and preserved ejection fraction, 850 patients (mean age, 75 years) recruited from 8 European countries were randomized to receive perindopril or placebo, and during 2.1 years of median follow-up, perindopril had no effect on the primary endpoint of all-cause mortality or heart failure hospitalization (hazard ratio {HR}, 0.92; p=0.545) or all-cause mortality (HR, 1.09; p=0.665).[13]

The non-significant effect of perindopril was explained in part by the unexpected low (45%) event rates and loss of power (from 90% to 35%) in PEP-CHF and a substantial open-label perindopril use after the first year of follow-up, before which perindopril tended to reduce the risk the primary endpoint (HR, 0.69; p=0.055) and significantly reduced the risk of heart failure hospitalization (HR, 0.63; p=0.033).[13] This early benefit of perindopril in PEP-CHF is similar to the early benefit of enalapril in patients with heart failure and reduced ejection fraction in the Studies of Left Ventricular Dysfunction (SOLVD) in which enalapril had no effect after second year of follow-up.[5] These observations, taken together with the neurohormonal activation in heart failure with preserved ejection fraction,[10] led us to hypothesize that ACE inhibitor use may be associated with improved outcomes in patients with heart failure and preserved ejection fraction, despite the definitive lack of efficacy of angiotensin receptor blockers in these patients. Therefore, the objective of the current study was to test this hypothesis in a propensity-matched (balanced)[14,15] inception cohort (new users)[16,17] of restricted (excluding those with contraindications to ACE inhibitors)[18,19] patients with heart failure and preserved ejection fraction.

MATERIALS AND METHODS

Data Sources and Study Population

The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) is a national registry of hospitalized heart failure patients and has been well described in the literature.[20-22] Briefly, charts from 48,612 hospitalizations due to heart failure occurring in 259 hospitals from 48 states between March 2003 and December 2004 were abstracted by trained staff.[20] A primary discharge diagnosis of heart failure was determined based on the International Classification of Diseases, 9th Revision codes 428, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, and 404.91.[22] Of the 48,612 hospitalizations, 20,839 were due to heart failure and preserved ejection fraction ≥40%. Extensive data on baseline demographics, medical history including admission and discharge medications including ACE inhibitors and angiotensin receptor blockers, hospital course, discharge disposition, and physician specialty were also collected.[22] Data on contraindications to the use of ACE inhibitors were also collected from patients not receiving these drugs. Missing values for continuous variables were imputed based on values predicted by age, sex and race.

Because OPTIMIZE-HF did not collect data on long-term outcomes, we linked OPTIMIZE-HF to Medicare outcomes data up to December 31, 2008, obtained from the Centers for Medicare and Medicaid Services.[23] Of the 20,839 heart failure hospitalizations due to heart failure and preserved ejection fraction, 13,270 could be linked to Medicare data. These events occurred in 11,997 unique patients, 10,889 of whom were 65 years or older,[24,25] of whom 10,570 were discharged alive (**Figure 1**). Because angiotensin receptor blockers have not been shown to improve outcomes in heart failure and preserved ejection fraction,[7,11,12,25] we excluded 1871 patients who received angiotensin receptor blockers. Of the remaining 8699 patients, 107 without data on discharge use of ACE inhibitors and another 1288 patients with contraindication to ACE inhibitors were excluded, leading to a final working sample size of 7304 patients who would be eligible for a discharge prescription for ACE inhibitors (**Figure 1**).

Assembly of an Inception Cohort

Because prevalent drug use may result in selection bias and left censoring,[16,17,26] we assembled an inception cohort of 4189 patients who were not receiving prior ACE inhibitor therapy and a discharge prescription for ACE inhibitors for these patients would be considered an initiation of therapy. Therefore, we excluded 3115 patients who received ACE inhibitors before hospital admission. Of the 4189 patients with no history of prior ACE inhibitor use or no contraindication to new ACE inhibitor therapy, 1706 (41%) received a new discharge prescription for ACE inhibitors (**Figure 1**).

Assembly of a Balanced Cohort

In well-designed randomized controlled trial, the probability of receiving a treatment is 50%, regardless of whether a patient is randomized to the treatment or the placebo group. However, treatment assignment in the real world is seldom random, and as such, these probabilities in non-randomized controlled trial studies would vary between 0 and 100%. These probabilities are often dictated by various measured and unmeasured patient and care characteristics. In real-world patients with heart failure, the probability of the receipt of an ACE inhibitor may be influenced by age, ejection fraction, blood pressure, serum potassium, serum creatinine, known adverse effects, and perceived or real contraindications. For example, 75 year-old patient with heart failure and preserved ejection fraction who have low blood pressure and high serum potassium will likely have a low probability of receiving ACE inhibitors, while 45 year-old patient with heart failure and reduced ejection fraction

who have normal blood pressure and normal serum potassium will likely have a high probability of receiving these drugs. These probabilities or propensity scores for the receipt of ACE inhibitors are predicted by data and may be similar in two patients. However, it is possible that one of these two patients actually received ACE inhibitor while the other patient did not. These two patients could then be matched to assemble a pair of patients receiving and not receiving ACE inhibitors who had similar predicted probabilities of receiving ACE inhibitors. In a properly conducted propensity-matched study, patients receiving and not receiving a treatment, such as an ACE inhibitor, would be balanced on all measured baseline characteristics.[14,27-31] Importantly, this balance can be achieved while remaining blinded to study outcomes, a key feature of randomized controlled trial.[27]

We used propensity scores for the receipt of ACE inhibitors to assemble our study cohort so that patients receiving and not receiving these drugs would be balanced on all measured baseline characteristics.[31-33] We estimated propensity scores for each of the 4189 patients using a non-parsimonious multivariable logistic regression model.[32,33] In the model, the receipt of ACE inhibitors was the dependent variable, and 114 baseline characteristics displayed in **Figure 2** were used as covariates. Although propensity scores can be used in regression models or for stratification, matching by propensity scores allows assembly of cohorts in which baseline balance can be estimated and displayed in visually pleasant tabular forms. We used a greedy matching protocol to match 1337 (78%) of the 1706 patients receiving ACE inhibitors with 1337 patients who did not receive ACE inhibitors but had the same propensity or probability to receive them.[34,35] The effectiveness of propensity score model was assessed by estimating absolute standardized differences,[15,28,36] and presented as a Love plot.[37-39] A difference of 0% indicates no residual bias and values <10% are considered inconsequential.

Mortality and Hospitalization

The primary outcome of the current analysis was the composite endpoint of all-cause mortality or heart failure hospitalization.[24] Secondary outcomes included all-cause mortality, heart failure and all-cause hospitalizations. Data on mortality and hospitalization were obtained from the 100% MedPAR File and 100% Beneficiary Summary File between January 1, 2002 and December 31, 2008.

Statistical Analysis

For descriptive analyses, we used Pearson's Chi-square and Wilcoxon rank-sum tests for the pre-match data, and McNemar's test and paired sample t-test for post-match comparisons, as appropriate. Because measured baseline characteristics are balanced in propensity-matched cohorts, we used bivariate Cox proportional hazard models to determine the associations of a new discharge prescription for ACE inhibitors (independent variable) with outcomes (dependent variable) among matched patients during 6 years of follow-up (median, and 25th and 75th percentiles, 2.4, 0.7 and 4.5 years, respectively). Log-minus-log survival plots were used to check proportional hazards assumptions. We conducted a formal sensitivity analysis to estimate the degree of hidden bias that could potentially explain away a significant association between ACE inhibitors and the primary composite outcome among our matched patients.[40] Subgroup analyses were conducted to determine the homogeneity of association between the use of ACE inhibitors and the composite primary outcome. Because an older cohort with a long follow-up will ultimately have 100% mortality, estimation of number needed to treat using absolute risk difference may be less useful. Therefore, using a formula proposed for survival analyses, we estimated number needed to treat with ACE inhibitors to prevent one primary composite endpoint event.[41] All statistical tests were two-tailed and 95% confidence intervals (CI) were constructed. Finally, we examined the association of ACE inhibitors with outcomes among pre-match patients using multivariable Cox regression

models adjusting for (1) all 114 baseline characteristics used in the propensity model and (2) propensity scores. All data analyses were performed using SPSS for Windows version 18 (SPSS, Inc., 2009, Chicago, IL).

RESULTS

Baseline Characteristics

Matched patients (n=2674) had a mean (±SD) age of 81 (±8) years, mean (±SD) LVEF of 55% (±9), 63% were women and 9% were African American. Before matching, patients receiving a new prescription for ACE inhibitors were more likely to be symptomatic but had lower prevalence of comorbidities such as atrial fibrillation and chronic kidney disease. These and other pre-match imbalances were balanced after matching (**Tables 1** and **2**, and **Figure 2**). Absolute standardized differences for all 114 baseline characteristics between the two treatment groups were <10% (mostly <5%) suggesting substantial bias reduction.

New Prescriptions for ACE Inhibitors and Outcomes

During 2.4 years of median follow-up, the primary composite endpoint of all-cause mortality or heart failure hospitalization occurred in 80% (1076/1337) and 83% (1112/1337) of matched patients with heart failure and preserved ejection fraction receiving and not receiving a new discharge prescription for ACE inhibitors, respectively, (hazard ratio {HR} when the use of ACE inhibitors was compared with their non-use, 0.91; 95% CI, 0.84–0.99; p=0.028; **Figure 3** and **Table 3**). An estimated 71 (95% CI, 40–646) patients will need to be treated over a median 2.4 years of follow-up to prevent one primary composite endpoint event. The association between new ACE inhibitor use and the primary composite endpoint was homogeneous across various subgroups of patients (**Figure 4**). ACE inhibitor use had no significant association with individual endpoints components of all-cause mortality and hospitalization (**Table 3**).

Among the 4189 pre-match patients, the primary composite endpoint occurred in 79% (1351/1706) and 84% (2079/2483) of patients receiving and not receiving a new discharge prescription for ACE inhibitors, respectively (HR, 0.84; 95% CI, 0.78–0.90; p<0.001). Multivariable-adjusted and propensity-adjusted HRs for primary composite endpoint associated with ACE inhibitor use were 0.93 (95% CI, 0.86–1.00; p=0.049) and 0.94 (95% CI, 0.87–1.01; p=0.098), respectively.

DISCUSSION

Findings from our study demonstrate that a new discharge prescription for ACE inhibitors was associated with a statistically significant modest 9% lower risk of the composite endpoint of all-cause mortality or heart failure hospitalization in a wide spectrum of propensity-matched older patients with heart failure and preserved ejection fraction who were balanced on over one hundred potential confounders. Similar multivariable-adjusted or propensity-adjusted associations were observed when traditional regression-based risk adjustment models were used in the pre-match cohort. However, ACE inhibitors had no significant association with individual endpoint components of all-cause mortality or heart failure hospitalization. Findings from the current rigorously-conducted propensity-matched inception cohort study based on nationally representative real-world patients provide evidence that the use of ACE inhibitors may be associated with a modest improvement in the long-term composite endpoint of total mortality or heart failure hospitalization in older patients with heart failure and preserved ejection fraction.

The 9% reduction in the composite endpoint in our study is substantially smaller than the 26% reduction in the same endpoint in younger systolic heart failure patients in the SOLVD trial.[5] In the SOLVD trial, enalapril seemed to have a more robust effect on heart failure hospitalization than on mortality which in part may also explain the overall benefit of ACE inhibitors in heart failure patients with preserved ejection fraction. The effect of ACE inhibitors may also be mediated by their beneficial effect on aortic stenosis, the prevalence of which would be expected to be high in older heart failure patients with preserved ejection fraction. The inhibition of the renin-angiotensin system has been shown to be associated with improved outcomes in patients with aortic stenosis.[42] The lack of significant association with all-cause mortality in our study may in part be explained by the different modes of death in heart failure patients with preserved versus reduced ejection fraction. Findings from major randomized controlled trial of ACE inhibitors in systolic heart failure suggest that these drugs had no significant effect on sudden cardiac death but had a robust effect on death due to pump failure.[5,6] While sudden death accounts for between 40% and 50% of cardiovascular deaths in heart failure patients regardless of ejection fraction, death due to pump failure is less common in those with preserved ejection fraction, accounting for 24% of cardiovascular deaths (versus 41% in those with reduced ejection fraction).[43] This may in part explain the lack of an effect of ACE inhibitors on mortality in patients with heart failure and preserved ejection.

Most randomized controlled trials of ACE inhibitors in heart failure excluded those with preserved ejection fraction. The overall direction and magnitude of the associations with primary endpoint observed in our study (9% reduction) are consistent with those from PEP-CHF (8% reduction).[13] A recent propensity-matched study of ACE inhibitors or angiotensin receptor blockers based on the Swedish Heart Failure Registry reported mortality reduction in patients with heart failure and preserved ejection fraction.[44] This association seems inflated as nearly 25% of patients in that study were receiving angiotensin receptor blockers, with proven lack of effect on mortality.[11,12] In addition, in PEP-CHF, perindopril had no effect on all-cause mortality, not even during the first year of follow-up, when it reduced heart failure hospitalization, suggesting lack of efficacy on mortality.[13] That study based on the Swedish Heart Failure Registry was also limited by biases due to lack of restriction to patients without contraindications,[18,19] lack of exclusion of prevalent drug users,[16,17] and incomplete matching,[45] as over a quarter of 43 variables used in propensity matching were imbalanced after matching.[44] Despite potential overestimation of the association in the Swedish Heart Failure Registry, findings from PEP-CHF and our study suggest that ACE inhibitor therapy may be associated with a very modest improvement in the long-term clinical outcomes in patients with heart failure and preserved ejection fraction. However, given the lack of benefit of angiotensin receptor blockers in those patients,[7,11,12,25] these findings need to be interpreted with caution and be replicated in other restricted propensity-matched inception cohorts.

Our study has several limitations. Findings from our sensitivity analysis suggest that this association could be potentially explained away by a hidden covariate that would increase the odds for the receipt of ACE inhibitors by about 1%. However, to act as a confounder, an unmeasured covariate must be a near-perfect predictor of outcome and also not be strongly correlated with any of the 114 measured baseline covariates used in our study, which is unlikely. We were able to match nearly 80% of patients receiving ACE inhibitors, thus minimizing any effect on external validity. We had no data on names and doses for individual ACE inhibitors. We also had no data on the use of ACE inhibitors after discharge.[46] Substantial crossover may result in regression dilution,[47] and may potentially explain the modest associations observed in our study. Lack of data on aortic stenosis is another limitation. The clinical data for the analyses were collected from the medical record and depended upon the accuracy and completeness of the clinical documentation. Although

this study is confined to fee-for-service Medicare patients and hospital participation in OPTIMIZE-HF was voluntary and limited to all those hospitals participating in a quality improvement registry and this may limit the generalizability of the results. However, Medicare-linked OPTIMIZE-HF patients have been shown to have similar characteristics and outcomes as heart failure patients in the general Medicare population.[48]

CONCLUSIONS

In hospitalized older patients with heart failure and preserved ejection fraction who were not receiving angiotensin receptor blockers, a new discharge prescription for ACE inhibitors was associated with a modest improvement in the composite endpoint of total mortality or heart failure hospitalization, but had no association with the individual components of mortality and heart failure hospitalization. Findings from this rigorously conducted propensity-matched inception cohort study need to be interpreted in the context of inconclusive findings from the PEP-CHF trial and proven lack of efficacy of angiotensin receptor blockers in these patients. Additional well-designed prospective studies are needed.

Acknowledgments

Funding/Support: The project described was supported by the grant R01-HL097047 from NHLBI/NIH (PI: Ahmed, A). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NHLBI or NIH. Dr. Ahmed is also supported by a generous gift from Ms. Jean B. Morris of Birmingham, Alabama. Dr. Allman is supported by NIH/NCRR grant 5UL1 RR025777. OPTIMIZE-HF was funded by GlaxoSmithKline (PI: Fonarow, GC).

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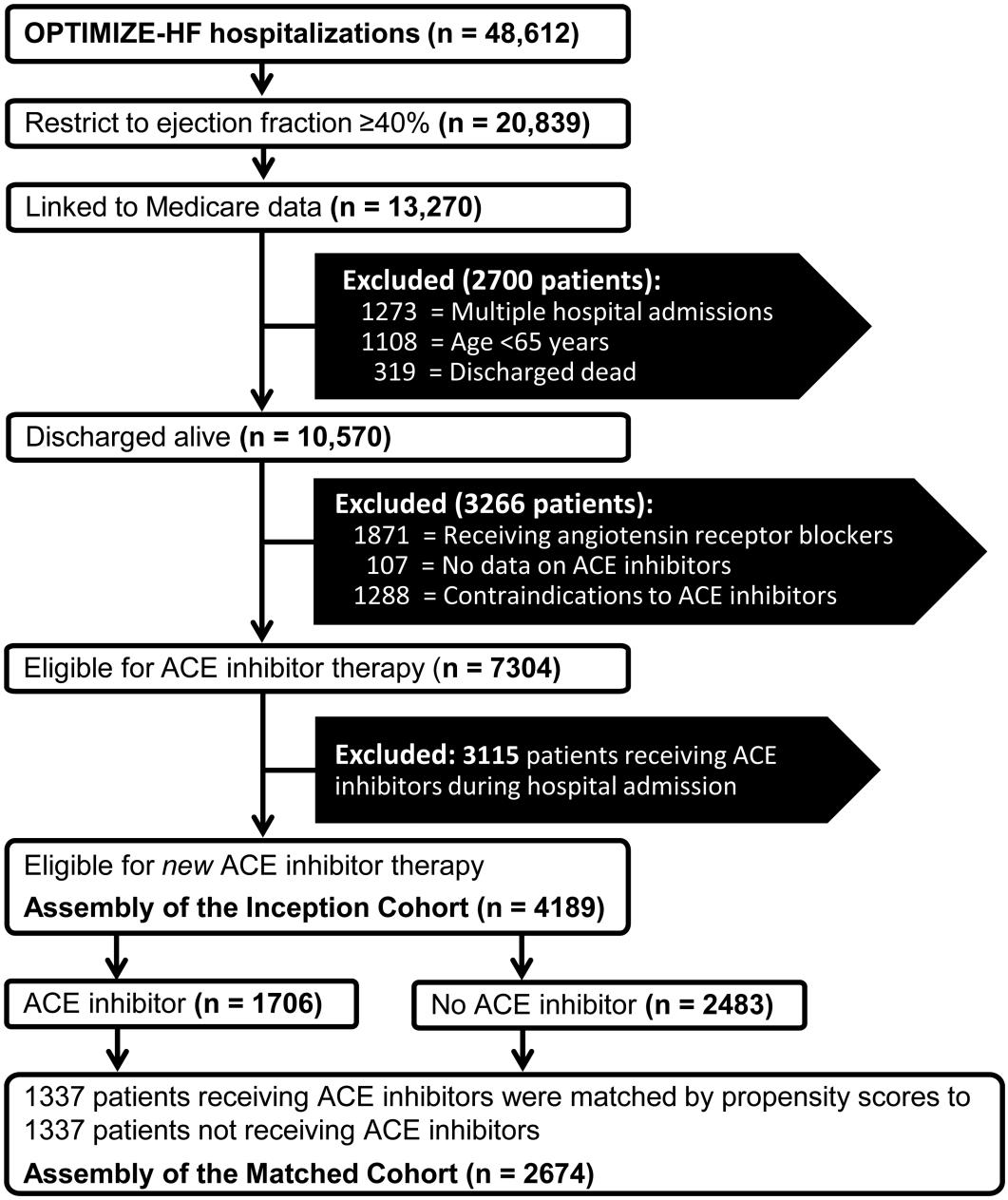


Figure 1.
Flow chart displaying assembly of the inception cohort of matched patients with heart failure and preserved ejection fraction. ACE = angiotensin-converting enzyme; OPTIMIZE-HF = Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure

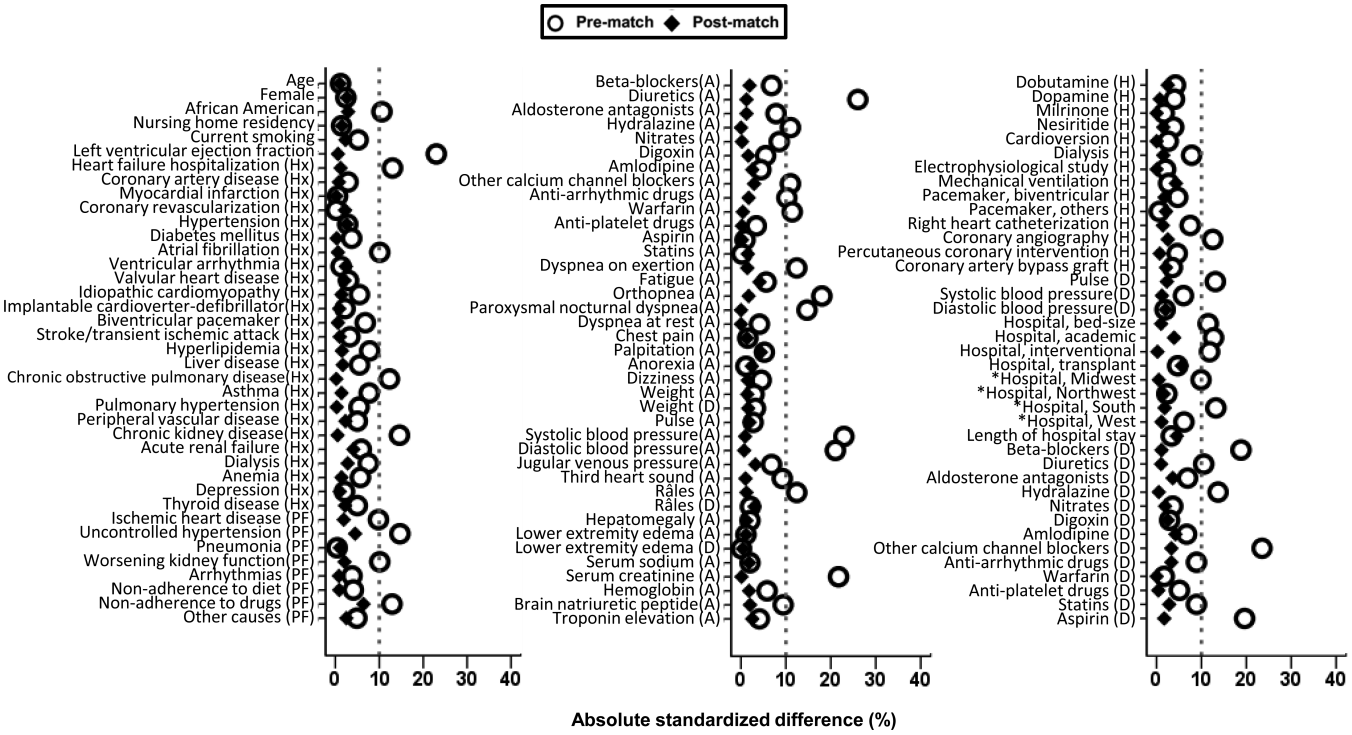
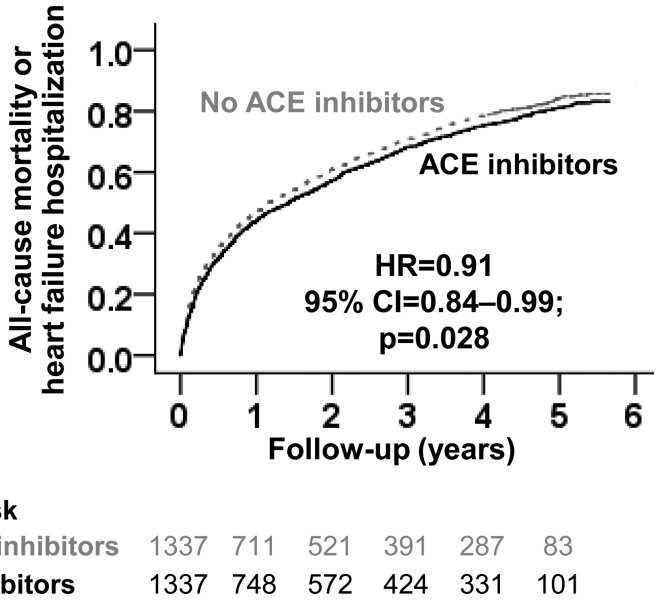


Figure 2.

Love plot displaying absolute standardized differences comparing 114 baseline characteristics between older patients with heart failure and preserved ejection fraction, receiving a new discharge prescription of angiotensin-converting enzyme inhibitors, before and after propensity score matching

(Hx = medical history, A = admission, D = discharge, H = in-hospital, PF = precipitating factor; *the total number of variables do not equal 114 as the 4 hospital regions were entered as a single categorical variable in the model)



No. at risk						
No ACE inhibitors	1337	711	521	391	287	83
ACE inhibitors	1337	748	572	424	331	101

Figure 3.

Kaplan-Meier plot for primary composite endpoint of all-cause mortality or heart failure hospitalization in a propensity-matched inception cohort of older patients with heart failure and preserved ejection fraction, receiving and not receiving a new discharge prescription for angiotensin-converting enzyme (ACE) inhibitors (HR = hazard ratio, CI = confidence interval)

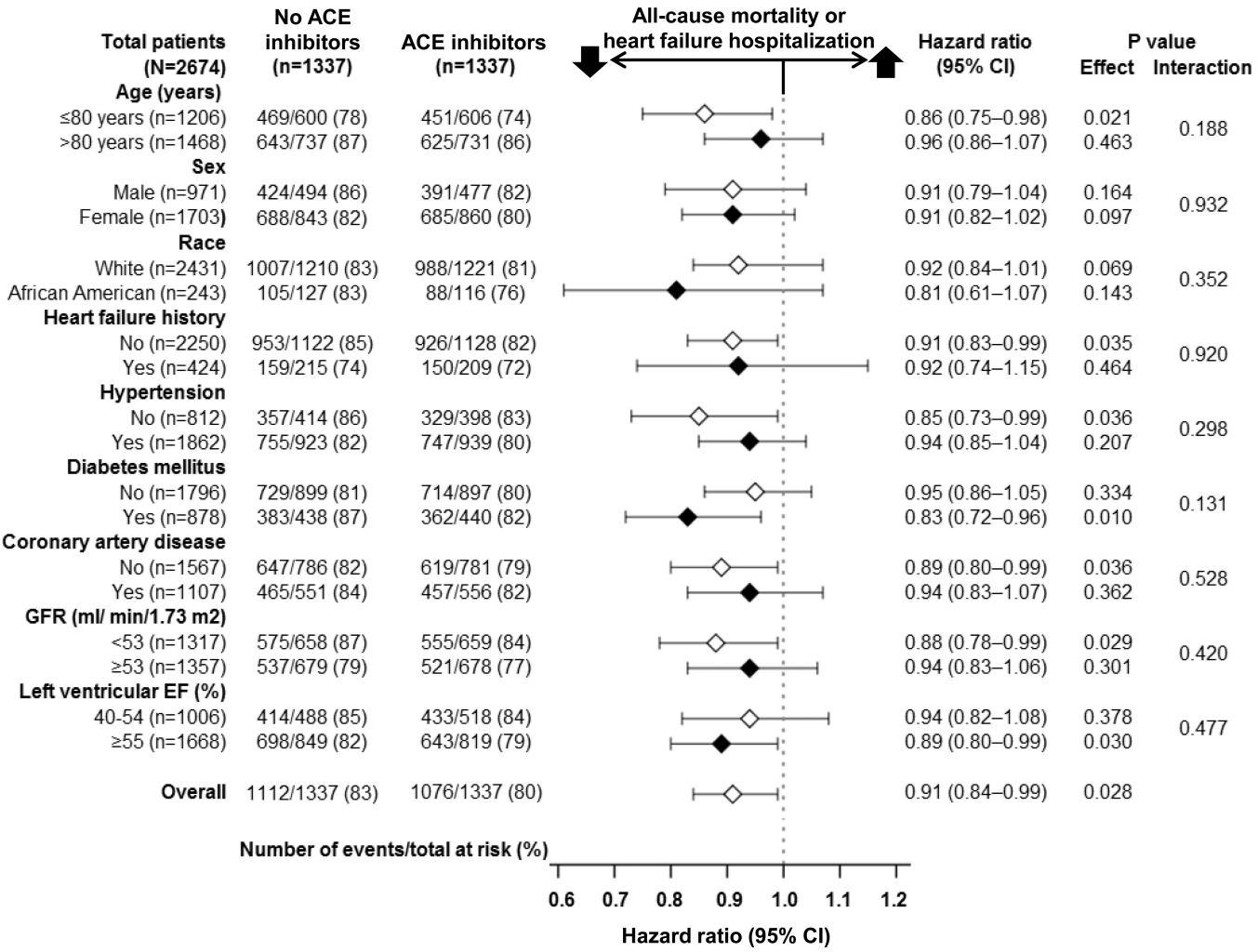


Figure 4.

Association of a new discharge prescription of angiotensin-converting enzyme (ACE) inhibitors with primary composite endpoint of all-cause mortality or heart failure hospitalization in subgroups of propensity-matched inception cohort of older patients with heart failure and preserved ejection fraction

Am J Med. Author manuscript; available in PMC 2014 May 01.

Table 1

Baseline patients and care characteristics of older patients with heart failure and preserved ejection fraction, by a new discharge prescription for angiotensin-converting enzyme (ACE) inhibitors

Variables Mean (SD) or n (%)	Before propensity score matching			After propensity score matching		
	Use of ACE Inhibitors		P value	Use of ACE Inhibitors		P value
	No (n=2483)	Yes (n=1706)		No (n=1337)	Yes (n=1337)	
Age (years)	81 (8)	81 (8)	0.713	81 (8)	81 (8)	0.793
Female	1611 (65)	1087 (64)	0.439	843 (63)	860 (64)	0.513
African American	184 (7)	174 (10)	0.001	127 (10)	116 (9)	0.503
Left ventricular ejection fraction (%)	56 (9)	54 (10)	<0.001	55 (9)	55 (10)	0.870
Precipitating factors for hospital admission						
Ischemic heart disease	242 (10)	219 (13)	0.002	160 (12)	152 (11)	0.676
Uncontrolled hypertension	166 (7)	185 (11)	<0.001	107 (8)	124 (9)	0.252
Worsening renal function	112 (5)	45 (3)	0.002	46 (3)	41 (3)	0.668
Arrhythmia	395 (16)	248 (15)	0.226	201 (15)	205 (15)	0.872
Non-adherence to diet	58 (2)	51 (3)	0.192	34 (3)	36 (3)	0.904
Non-adherence to medications	88 (4)	108 (6)	<0.001	54 (4)	72 (5)	0.117
Past Medical History						
No prior heart failure hospitalization	348 (14)	321 (19)	<0.001	215 (16)	209 (16)	0.786
Coronary artery disease	1047 (42)	695 (41)	0.357	551 (41)	556 (42)	0.875
Hypertension	1722 (69)	1205 (71)	0.374	923 (69)	939 (70)	0.538
Diabetes mellitus	842 (34)	549 (32)	0.243	438 (33)	440 (33)	0.968
Atrial fibrillation	972 (39)	585 (34)	0.001	489 (37)	493 (37)	0.906
Hyperlipidemia	662 (27)	515 (30)	0.013	385 (29)	394 (30)	0.729
Chronic obstructive pulmonary disease	804 (32)	457 (27)	<0.001	378 (28)	377 (28)	1.000
Peripheral vascular disease	334 (14)	201 (12)	0.112	155 (12)	165 (12)	0.598
Chronic kidney disease	1608 (65)	984 (58)	<0.001	798 (60)	795 (60)	0.937
Admission symptoms & signs						
Dyspnea on exertion	1465 (59)	1109 (65)	<0.001	846 (63)	837 (63)	0.747
Fatigue	567 (23)	350 (21)	0.074	267 (20)	289 (22)	0.317
Orthopnea	493 (20)	469 (28)	<0.001	331 (25)	321 (24)	0.686
Paroxysmal nocturnal dyspnea	243 (10)	249 (15)	<0.001	168 (13)	168 (13)	1.000

Variables Mean (SD) or n (%)	Before propensity score matching			After propensity score matching		
	Use of ACE Inhibitors		P value	Use of ACE Inhibitors		P value
	No (n=2483)	Yes (n=1706)		No (n=1337)	Yes (n=1337)	
Dyspnea at rest	1048 (42)	755 (44)	0.188	582 (44)	582 (44)	1.000
Chest pain	510 (21)	361 (21)	0.627	277 (21)	284 (21)	0.779
Pulse (beats/minute)	85 (22)	85 (21)	0.390	85 (22)	84 (21)	0.630
Systolic blood pressure (mm Hg)	144 (30)	151 (31)	<0.001	148 (31)	148 (29)	0.807
Diastolic blood pressure (mm Hg)	73 (17)	77 (19)	<0.001	75 (18)	75 (18)	0.865
Jugular venous pressure elevation	614 (25)	473 (28)	0.030	370 (28)	351 (26)	0.435
Third heart sound	118 (5)	118 (7)	0.003	76 (6)	73 (6)	0.865
Pulmonary rales	1485 (60)	1122 (66)	<0.001	839 (63)	847 (63)	0.775
Lower extremity edema	1621 (65)	1105 (65)	0.732	873 (65)	866 (65)	0.806
Laboratory values						
Serum sodium (mEq/L)	137 (10)	137 (11)	0.529	137 (11)	137 (10)	0.647
Serum creatinine (mg/dL)*	1.20 (0.70)	1.10 (0.60)	<0.001	1.20 (0.70)	1.20 (0.60)	0.980
Serum hemoglobin (g/dL)	11.9 (2.1)	12.0 (2.1)	0.067	12.0 (2.0)	11.9 (2.1)	0.639
Serum brain natriuretic peptide, (pg/mL)*	740 (690.82)	806 (773.18)	0.003	753 (717.50)	780 (744.68)	0.604
Serum troponin elevation†	359 (15)	272 (16)	0.187	194 (15)	206 (15)	0.546
Length of hospital stay	6 (5)	14 (354)	0.242	6 (5)	6 (4)	0.245
Hospital characteristics						
Bed size*	350 (221)	375 (200)	<0.001	355 (212)	360 (207)	0.790
Academic	985 (40)	784 (46)	<0.001	604 (45)	578 (43)	0.334
Interventional	1816 (73)	1334 (78)	<0.001	1030 (77)	1031 (77)	1.000
Transplant	363 (15)	222 (13)	0.141	201 (15)	175 (13)	0.161
Hospital location by region						
Midwest	702 (28)	560 (33)	<0.001	416 (31)	419 (31)	0.776
Northeast	420 (17)	274 (16)		232 (17)	224 (17)	
South	879 (35)	499 (29)		402 (30)	413 (31)	
West	482 (19)	373 (22)		287 (22)	281 (21)	

*Displayed as median (interquartile range)

† Determined by local laboratories

Table 2

Procedures and treatment in older patients with heart failure and preserved ejection fraction, by a new discharge prescription for angiotensin-converting enzyme (ACE) inhibitors

Variables Mean (SD) or n (%)	Before propensity score matching			After propensity score matching		
	Use of ACE Inhibitors		P value	Use of ACE Inhibitors		P value
	No (n=2483)	Yes (n=1706)		No (n=1337)	Yes (n=1337)	
Admission medication						
Beta-blockers	1168 (47)	745 (44)	0.031	634 (47)	621 (46)	0.639
Aldosterone antagonists	104 (4)	47 (3)	0.014	47 (4)	44 (3)	0.828
Angiotensin receptor blockers*	–	–	–	–	–	–
Diuretics	1538 (62)	838 (49)	<0.001	732 (55)	724 (54)	0.778
Digoxin	453 (18)	276 (16)	0.083	223 (17)	231 (17)	0.717
Hydralazine	73 (3)	23 (1)	0.001	20 (2)	20 (2)	1.000
Nitrates	467 (19)	266 (16)	0.007	219 (16)	220 (17)	1.000
Amlodipine	230 (9)	137 (8)	0.166	103 (8)	112 (8)	0.573
Non-amlodipine calcium channel blockers	480 (19)	259 (15)	0.001	196 (15)	210 (16)	0.476
Anti-arrhythmic drugs	233 (9)	113 (7)	0.001	101 (8)	95 (7)	0.711
Warfarin	584 (24)	322 (19)	<0.001	284 (21)	286 (21)	0.963
Anti-platelet drugs	267 (11)	166 (10)	0.285	141 (11)	140 (11)	1.000
Aspirin	869 (35)	590 (35)	0.782	479 (36)	478 (36)	1.000
Statins	638 (26)	437 (26)	0.954	365 (27)	356 (27)	0.730
In-hospital treatment/procedure						
Dobutamine	20 (1)	21 (1)	0.169	12 (1)	9 (1)	0.664
Dopamine	51 (2)	26 (2)	0.210	16 (1)	17 (1)	1.000
Milrinone	9 (0.4)	8 (0.5)	0.594	6 (0.4)	6 (0.4)	1.000
Nesiritide	190 (8)	114 (7)	0.235	88 (7)	93 (7)	0.762
Right heart catheterization	48 (2)	53 (3)	0.015	35 (3)	38 (3)	0.813
Coronary angiography	117 (5)	132 (8)	<0.001	77 (6)	85 (6)	0.578
Coronary artery bypass grafting	12 (0.5)	13 (0.8)	0.250	8 (0.6)	6 (0.4)	0.791
Percutaneous coronary intervention	18 (1)	20 (1)	0.133	14 (1)	13 (1)	1.000
Electrophysiological study	17 (1)	9 (1)	0.525	8 (1)	8 (1)	1.000

Variables Mean (SD) or n (%)	Before propensity score matching			After propensity score matching		
	Use of ACE Inhibitors		P value	Use of ACE Inhibitors		P value
	No (n=2483)	Yes (n=1706)		No (n=1337)	Yes (n=1337)	
Cardioversion	30 (1)	16 (1)	0.409	14 (1)	14 (1)	1.000
Pacemaker-biventricular	9 (0.4)	12 (0.7)	0.125	8 (1)	10 (1)	0.815
Dialysis	82 (3)	35 (2)	0.016	29 (2)	32 (2)	0.788
Discharge medication						
Beta-blockers	1318 (53)	1603 (62)	<0.001	790 (59)	783 (59)	0.811
Aldosterone antagonists	179 (7)	155 (9)	0.028	99 (7)	112 (8)	0.385
Angiotensin receptor blockers*	–	–	–	–	–	–
Diuretics	1932 (78)	1399 (82)	0.001	1079 (81)	1084 (81)	0.842
Digoxin	543 (22)	394 (23)	0.349	290 (22)	304 (23)	0.553
Hydralazine	94 (4)	27 (2)	<0.001	27 (2)	26 (2)	1.000
Nitrates	562 (23)	412 (24)	0.254	329 (25)	318 (24)	0.650
Amlodipine	223 (9)	122 (7)	0.034	95 (7)	110 (8)	0.311
Non-amlodipine calcium channel blockers	500 (20)	198 (12)	<0.001	167 (13)	182 (14)	0.410
Anti-arrhythmic drugs	283 (11)	149 (9)	0.005	137 (10)	124 (9)	0.434
Warfarin	669 (27)	447 (26)	0.594	366 (27)	366 (27)	1.000
Anti-platelet drugs	298 (12)	234 (14)	0.102	178 (13)	176 (13)	0.955
Aspirin	996 (40)	850 (50)	<0.001	616 (46)	605 (45)	0.687
Statins	646 (26)	512 (30)	0.005	398 (30)	381 (29)	0.487

*Patients receiving angiotensin receptor blockers on admission and during discharge were excluded

Am J Med. Author manuscript; available in PMC 2014 May 01.

Table 3

Outcomes by a new discharge prescription for angiotensin-converting enzyme (ACE) inhibitors in a propensity-matched inception cohort of older patients with heart failure and preserved ejection fraction

Outcomes	Events (%)		Hazard ratio* (95% confidence interval)	P value
	No ACE Inhibitors (n=1337)	ACE Inhibitors (n=1337)		
Combined endpoint of all-cause mortality or heart failure hospitalization	1112 (83%)	1076 (80%)	0.91 (0.84–0.99)	0.028
All-cause mortality	951 (71%)	930 (70%)	0.96 (0.88–1.05)	0.373
Heart failure hospitalization	564 (42%)	558 (42%)	0.93 (0.83–1.05)	0.257
All-cause hospitalization	1155 (86%)	1165 (87%)	0.97 (0.89–1.05)	0.401

*Hazard ratios comparing patients receiving ACE inhibitors versus those not receiving ACE inhibitors calculated using Cox regression model