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Aldosterone Antagonists and Outcomes in Real-World Older Patients with Heart Failure and Preserved Ejection Fraction

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Abstract

Objectives—The purpose of this study was to examine the clinical effectiveness of aldosterone antagonists in older patients with heart failure and preserved ejection fraction (HF-PEF).

Background—Aldosterone antagonists improve outcomes in HF and reduced EF. However, their role in HF-PEF remains unclear.

Methods—Of the 10,570 hospitalized older (age ≥65 years) HF-PEF (EF ≥40%) patients in Medicare-linked OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) trial, 8013 had no prior aldosterone antagonist use and no current contraindications, of whom 492 (6% of 8013) received new prescriptions for aldosterone antagonists. We assembled a matched cohort of 487 pairs of patients receiving and not receiving aldosterone antagonists, who had similar propensity to receive these drugs, and were balanced on 116 baseline characteristics.

Results—Patients had a mean age of 80 years, a mean EF of 54%, 59% were women, and 8% were African American. During 2.4 year of mean follow-up (through December, 2008), the

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primary composite endpoint of all-cause mortality or HF hospitalization occurred in 392 (81%) and 393 (81%) patients receiving and not receiving aldosterone antagonists, respectively (hazard ratio {HR}, 0.97; 95% confidence interval {CI}, 0.84–1.11; p=0.628). Aldosterone antagonists had no association with all-cause mortality (HR, 1.03; 95% CI, 0.89–1.20; p=0.693) or HF hospitalization (HR, 0.88; 95% CI, 0.73–1.07; p=0.188). Among 8013 pre-match patients, multivariable-adjusted HR for primary composite endpoint associated with aldosterone antagonist use was 0.93 (95% CI, 0.83–1.03; p=0.144).

Conclusions—In older HF-PEF patients, aldosterone antagonists had no association with clinical outcomes. Findings from the ongoing randomized controlled TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial will provide further insights into their effect in HF-PEF.

Keywords

Aldosterone antagonists; Heart failure; Preserved ejection fraction

Aldosterone antagonists have been shown to reduce the risk of mortality and hospitalization in heart failure and reduced ejection fraction (HF-REF) (1-3). HF and preserved ejection fraction (HF-PEF) comprise nearly half of all HF patients, and have similar prognosis as for HF-REF (4,5). Because activation of the mineralocorticoid receptor by aldosterone may be associated with pathophysiologic changes in HF-PEF such as myocardial fibrosis, left ventricular hypertrophy, renal fibrosis, and vascular injury, this may be a key therapeutic target in these patients (6). Further, these drugs have been shown to reduce myocardial fibrosis and improve diastolic function in HF-PEF (7,8). However, the role of aldosterone antagonists on clinical outcomes in HF-PEF remains unclear.

The effect of spironolactone, an aldosterone antagonist, on morbidity, mortality, and quality of life in patients with HF-PEF is currently being studies in the ongoing multi-center, randomized, double-blind, placebo-controlled Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist (TOPCAT) trial (9). Propensity-matched studies can be a tool for deriving bridge evidence when randomized clinical trial (RCT) based evidence is not readily available (10,11). Further, real-world HF patients are often characteristically and prognostically different from those enrolled in RCTs (12,13). Therefore, in the current study, we examined clinical effectiveness of aldosterone antagonists in real-world older HF-PEF patients.

Methods

Data sources and study population

The OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) is a national registry of hospitalized HF patients, the details of the design and implementation of which have been previously reported (14-16). Briefly, extensive data on baseline demographics, medical history including admission and discharge medications, hospital course, and discharge disposition were collected by chart abstraction from 48,612 hospitalizations due to HF occurring in 259 hospitals in 48 states during March 2003 – December 2004 (14). A primary discharge diagnosis of HF was based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes for HF (14,15). Considering that HF patients with EF 40% to 50% are characteristically and prognostically similar to those with EF >50% (5), we used EF ≥40% to define HF-PEF and of the 48,612 HF hospitalizations, 20,839 occurred in those with HF-PEF. To obtain long-term outcomes data, we linked OPTIMIZE-HF to Medicare claims data consisting of 100% Medicare Provider Analysis and Review (MedPAR) File and 100%

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Beneficiary Summary File between January 1, 2002 and December 31, 2008. We were able to link 13,270 of the 20,839 HF-PEF hospitalizations to Medicare data, occurring in 11,997 unique patients, of whom 10,889 were ≥65 years, and 10,570 were discharged alive (13).

Assembly of an eligible cohort

Data on admission and discharge use of aldosterone antagonists and other key HF medications were collected by chart abstraction. Except for beta-blockers, data on individual drugs and dosages were not available for other drugs including aldosterone antagonists. To assemble a cohort eligible for aldosterone antagonist therapy, we excluded patient who had contraindications to the use of these drugs. As such, patients with impaired renal function, defined as serum creatinine of >2.5 mg/dl in males and >2.0 mg/dl in females (n=1443), and an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 (n=602) were excluded (17). In addition, 193 patients receiving both angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) were excluded (18). Because data on admission serum potassium were unavailable, we also excluded 91 patients whose pre-admission aldosterone antagonist was discontinued before hospital discharge. Thus, after excluding a total of 2329 patients with potential contraindications and intolerance, the remaining 8241 patients were considered eligible for discharge aldosterone antagonist therapy.

Assembly of an inception cohort

Because the receipt of study drug prior to study baseline may affect baseline characteristics and may also causes left censoring, both potentially leading to selection bias, we assembled an inception cohort of patients who had not received aldosterone antagonists in the past (19-21). This was achieved by excluding 228 patients who were receiving aldosterone antagonists during admission. Thus, the final sample size for our inception cohort consisted of 8013 hospitalized patients not receiving aldosterone antagonists and of these, 492 (6.1%) received a new discharge prescription of aldosterone antagonist.

Assembly of a balanced cohort

Because of the significant imbalances in many prognostically important baseline characteristics between patients receiving and not receiving a new discharge prescription for aldosterone antagonists (Table 1 and Figure 1), we used propensity scores for the receipt of aldosterone antagonists to assemble a cohort in which the two treatment groups would be balanced on all measured baseline characteristics (22-24). We estimated propensity scores for each of the 8013 patients using a non-parsimonious multivariable logistic regression model, in which the receipt of aldosterone antagonists was the dependent variable, and 116 baseline characteristics were used as covariates (25-27). Using a greedy matching protocol, we were able to match 487 of the 492 patients receiving aldosterone antagonists with another 487 patients not receiving these drugs but had similar propensity to receive them (28,29).

Propensity score models are sample-specific adjusters and are not intended to be used for out-of-sample prediction or estimation of coefficients. Therefore, measures of fitness and discrimination are not important for the assessment of these models' effectiveness. Instead, the efficacy of propensity score models is best assessed by estimating between-group post-match absolute standardized differences of baseline characteristics. Absolute standardized differences directly quantify bias in the means (or proportions) of covariates across the two treatments or exposure groups; a difference of 0% indicates no residual bias and values <10% are considered inconsequential. Therefore, we assessed the effectiveness of our propensity score model by estimating absolute standardized differences, which were presented as a Love plot (30,31).

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We replicated the above process to assemble a second balanced propensity-matched cohort in which HF-PEF was defined EF ≥50%. Finally, to determine clinical effectiveness of any (new or continuation) discharge prescription of aldosterone antagonists, we repeated the above process in 8241 patients eligible for aldosterone antagonist therapy, of whom 720 (9%) received discharge prescriptions to initiate or continue their aldosterone antagonists. We were able to match 712 of the 720 patients receiving aldosterone antagonists with another 712 patients not receiving these drugs thus assembling a third balanced propensity-matched cohort.

Outcomes

The primary outcome for the current analysis was a composite endpoint of all-cause mortality or HF hospitalization during about 6 years of follow-up (mean, 2.4 years, median, 1.4 years). Secondary outcomes included all-cause mortality, HF hospitalization, and all-cause hospitalization. All outcomes data were obtained from Medicare claims data (13,32). Medicare-linked OPTIMIZE-HF patients have been shown to be characteristically and prognostically similar to HF patients in the general Medicare population (32).

Statistical analysis

Baseline characteristics were compared using Pearson's Chi-square and Wilcoxon rank-sum tests for pre-match, and McNemar's test and paired sample t-test for post-match comparisons, as appropriate. Kaplan-Meier plots and Cox regression analyses were used to determine associations of discharge prescriptions of aldosterone antagonists with outcomes. To determine the homogeneity of association between aldosterone antagonist use and the primary endpoint, we conducted subgroup analyses. A formal sensitivity analysis was conducted to estimate the degree of hidden bias that could potentially explain away a significant association among matched patients (33). We repeated our analyses in the pre-match cohort using three different approaches: (1) unadjusted; (2) multivariable-adjusted, using all 116 baseline characteristics; and (3) propensity score-adjusted. All statistical tests were two-tailed with a p-value <0.05 considered significant. SPSS for Windows version 20 (Release 2011, IBM Corp. Armonk, NY) was used for data analysis.

Results

Baseline characteristics

Matched patients (n=974) had a mean (±SD) age of 80 (±7) years, a mean (±SD) left ventricular ejection fraction (LVEF) of 54% (±9%), 59% were women, and 8% were African American. Patients receiving aldosterone antagonists had lower mean LVEF, a higher symptom burden, and more likely to receive other neurohormonal antagonists, but no difference in blood pressure or serum creatinine (Table 1 and Figure 1). After matching, patients receiving and not receiving a new discharge prescription for aldosterone antagonists were balanced on 116 baseline characteristics. All post-match absolute standardized differences were <10% suggesting that all 116 measured baseline characteristics were balanced between the two treatment groups.

New discharge prescriptions for aldosterone antagonists and outcomes

During 2.4 years of mean follow-up, the primary composite endpoint of all-cause mortality or HF hospitalization occurred in 392 (81% of 487) and 393 (81% of 487) of matched patients receiving and not receiving a new discharge prescription of aldosterone antagonists, respectively (hazard ratio {HR} associated with aldosterone antagonist use, 0.97; 95% confidence interval {CI}, 0.84–1.11; p=0.628; Figure 2 and Table 2). This association was rather homogeneous across various clinically relevant subgroups of patients (Figure 3).

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Similar association was observed when the Cox model was stratified by matching (HR, 0.93; 95% CI, 0.78–1.12; p=0.933). There was no significant association with the primary composite endpoint at the end of first and second year of follow-up. Aldosterone antagonists had no significant association with all-cause mortality, HF or all-cause hospitalization (Table 2). All associations were similar, when EF >50% was used to define HF-PEF.

Among the 8013 pre-match patients, the primary composite endpoint occurred in 81% (397/492) and 82% (6126/7521) of patients receiving and not receiving a new discharge prescription of aldosterone antagonists, respectively (HR associated with aldosterone antagonists use, 0.96; 95% CI, 0.87–1.07; p=0.452). Corresponding multivariable-adjusted and propensity score-adjusted HRs were 0.93 (95% CI, 0.83–1.03; p=0.144) and 0.95 (95% CI, 0.86–1.05; p=0.324), respectively.

Any (new or continuation) prescription for aldosterone antagonists and outcomes

The primary composite endpoint of all-cause mortality or HF hospitalization occurred in 82% (587/712) of patients receiving any (new or continuation) discharge prescription for aldosterone antagonists versus 82% (583/712) of those not receiving any aldosterone antagonists (HR associated with aldosterone antagonists use, 1.00; 95% CI, 0.89–1.12; p=0.991; Table 2). Among the 8241 pre-match patients, unadjusted, multivariable-adjusted and propensity score-adjusted HRs (95% CIs) for the primary composite endpoint associated with any (new or continuation) use of aldosterone antagonists were 1.04 (0.96–1.14; p=0.311), 0.97 (0.89–1.06; p=0.492), and 0.98 (0.90–1.07; p=0.609), respectively. A discharge prescription for aldosterone antagonists (new or continuation) had no significant association with all-cause mortality or hospitalization among matched patients (Table 2). Similar associations were observed in patients using EF >50% to define HF-PEF.

Discussion

Findings from the current analysis demonstrate that a new discharge prescription for aldosterone antagonists had no unadjusted or independent association with any clinically important long-term outcomes in a wide spectrum of older HF-PEF patients who were balanced on over one hundred potential baseline characteristics and over 80% of whom experienced a primary endpoint event during six years of follow-up. Currently, there is no RCT evidence that aldosterone antagonists may improve outcomes in patients with HF-PEF. Findings from this rigorously conducted propensity-matched inception cohort study based on a nationally representative sample of real-world HF-PEF patients provide important insights about the potential role of aldosterone antagonists in HF-PEF. However, more definitive conclusions cannot be reached on the role of aldosterone antagonists in patients with HF-PEF until the TOPCAT trial results are available.

Aldosterone, a mineralocorticoid receptor agonist, is known to cause fibrosis and hypertrophy of the myocardium and be associated with poor cardiovascular outcomes (6). Spironolactone and eplerenone, drugs that block aldosterone receptors, on the other hand, have been shown to improve clinical outcomes in patients with HF-REF (1-3). As in HF-REF, HF-PEF is also associated with neurohormonal activation and myocardial fibrosis (34). However, findings from the current study suggest that unlike in HF-REF, these drugs may not improve clinical outcomes in HF-PEF. This is rather intriguing, as in the RALES (Randomized Aldactone Evaluation Study) trial, spironolactone significantly reduced both total mortality and HF hospitalization in HF-REF (1) and in the EMPHASIS (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trial significantly reduced the composite endpoint of total mortality or HF hospitalization in HF-REF (3). Although OPTIMIZE-HF did not collect data on individual aldosterone antagonists, a post hoc analysis of a similar cohort suggests that spironolactone was the most common aldosterone

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antagonists during the study period (35). Further, the use of eplerenone has been shown to reduce myocardial fibrosis and improve left ventricular remodeling in several mechanistic studies in human HF-PEF (7,8).

The discordant effect of aldosterone antagonists in HF-PEF (vis-à-vis HF-REF) is not implausible as ACE inhibitors and ARBs, effective in HF-REF, also do not seem to improve clinical outcomes in HF-PEF (36-38). One potential explanation may lie in the differential modes of death between HF-PEF and HF-REF. While cardiovascular and HF deaths are more common in HF-REF, it is much less common in HF-PEF (39). The lack of unadjusted associations between aldosterone antagonist use and outcomes in our pre-match cohort is also intriguing and rather unusual in observational studies. One potential explanation is that because aldosterone antagonists are not recommended for use in HF-PEF, any potential selection bias was limited. However, contraindications for aldosterone antagonists such as hyperkalemia and renal insufficiency would be expected to similar in HF-PEF and HF-REF and exclusion of patients with contraindication would have selected a healthier cohort via bias by indication. Another potential explanation is regression dilution and underestimation of associations due to crossover of therapy during follow-up (40). Although data on post-discharge adherence were not available, such crossover would be expected to be modest (41), and unlikely to fully nullify true associations. Finally, as in any observational study, chance, bias and confounding are potential alternate explanations, but unlikely given the observed null associations. Similarly, bias due to unmeasured confounders is also unlikely, although it could be not estimated as the null association precluded formal sensitivity analysis.

Several smaller mechanistic studies of aldosterone antagonists in HF-PEF that have examined other endpoints which demonstrated mixed results. In one study of 44 patients with HF-PEF, therapy with eplerenone, an aldosterone antagonist, was associated with attenuation of myocardial fibrosis and improvement of diastolic function at 12 months but had no effect on clinical variables or brain natriuretic peptide (8). In another study of 44 HF-PEF patients, eplerenone similarly improved myocardial fibrosis and diastolic function but had no effect of exercise capacity (7). One clinical study also did not find any multivariable-adjusted association between aldosterone and outcome in HF-PEF (42). In contrast to those studies, the current study is distinguished by its use of robust methodology (propensity matching and inception cohort design), high event rates and long-term follow-up. Currently there is no RCT-evidence of benefit of aldosterone antagonists in HF-PEF and the findings from our study provide interim evidence regarding the role of these drugs in HF-PEF. The efficacy of aldosterone antagonists in HF-PEF is being studied in the ongoing TOPCAT trial, which is expected to be completed by July 2013 (9).

Our study has several limitations. Although we excluded patients receiving aldosterone antagonists during hospital admission, we had no data on remote use. However, misclassification of remote users as nonusers is unlikely to introduce any bias as aldosterone antagonists are often discontinued for reasons of renal insufficiency and hyperkalemia. HF hospitalization was not centrally adjudicated and cause-specific mortality data were not available. The analyses were restricted to fee-for-service older Medicare patients and hospital participation in OPTIMIZE-HF was voluntary. Finally, data for the current analysis were collected from medical records and thus dependent on the accuracy and completeness of clinical documentation.

Conclusions

A new discharge prescription for aldosterone antagonists had no association with mortality or HF hospitalization as composite or individual endpoints in real-world hospitalized older

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patients with HF-PEF. Whether these results would differ from trial-eligible ambulatory younger HF-PEF patients will await results of the ongoing randomized controlled TOPCAT trial.

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Abbreviations

HF-REF	Heart failure and reduced ejection fraction
HF-PEF	Heart failure and preserved ejection fraction
TOPCAT	Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist
RCT	Randomized clinical trial
OPTIMIZE-HF	Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure
ACE inhibitors	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin receptors blockers
HR	Hazard ratio
CI	Confidence interval

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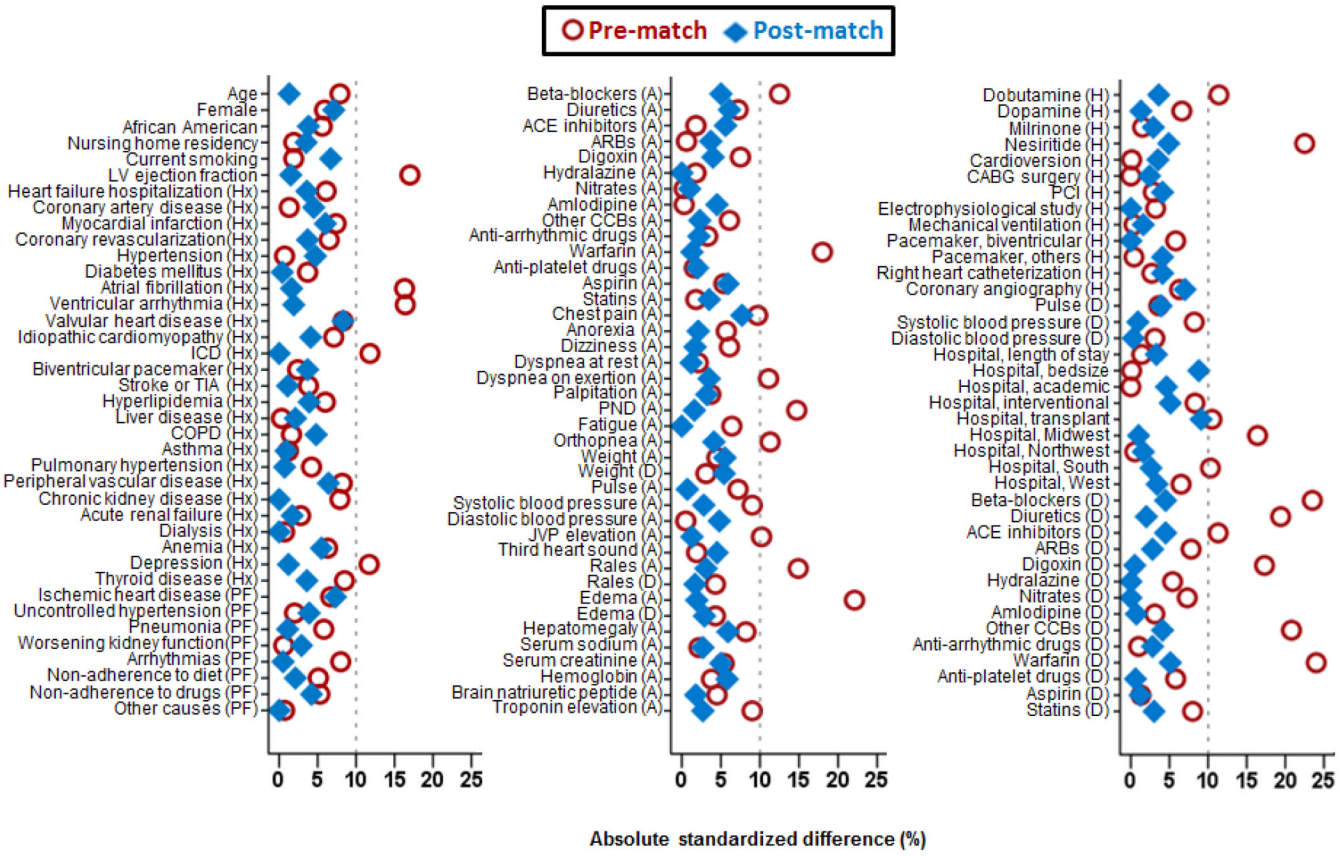

Figure 1. Love plot for absolute standardized differences

Love plot displaying absolute standardized differences comparing 116* baseline characteristics between older HF-PEF patients receiving new discharge prescriptions for aldosterone antagonists and not receiving any aldosterone antagonists, before and after propensity score matching. (Hx=past medical history, A=admission, D=discharge, H=in-hospital, PF=precipitating factor, ACE=angiotensin-converting enzyme, ICD=Implantable cardioverter-defibrillator, ARB=angiotensin receptor blocker, CABG=coronary artery bypass grafting, CCB=calcium channel blocker, COPD=chronic obstructive pulmonary disease, JVP=jugular venous pressure, PCI=percutaneous coronary intervention, PND=paroxysmal nocturnal dyspnea, TIA=transient ischemic attack; *4 regions entered as a single categorical variable in the model, dialysis during hospitalization was in the model but excluded from figure as there was no cases in the matched data)

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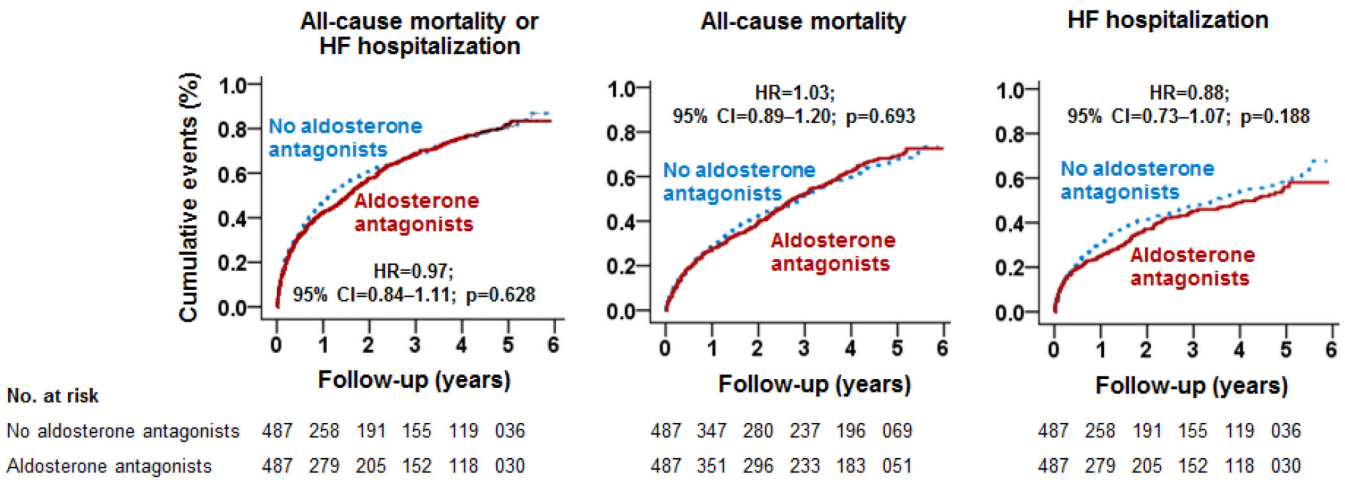

Figure 2. Kaplan-Meier plots for outcomes

Kaplan-Meier plots of outcomes in a propensity-matched inception cohort of older HF-PEF patients receiving new discharge prescriptions for aldosterone antagonists and not receiving any aldosterone antagonists (HR=hazard ratio, CI=confidence interval)

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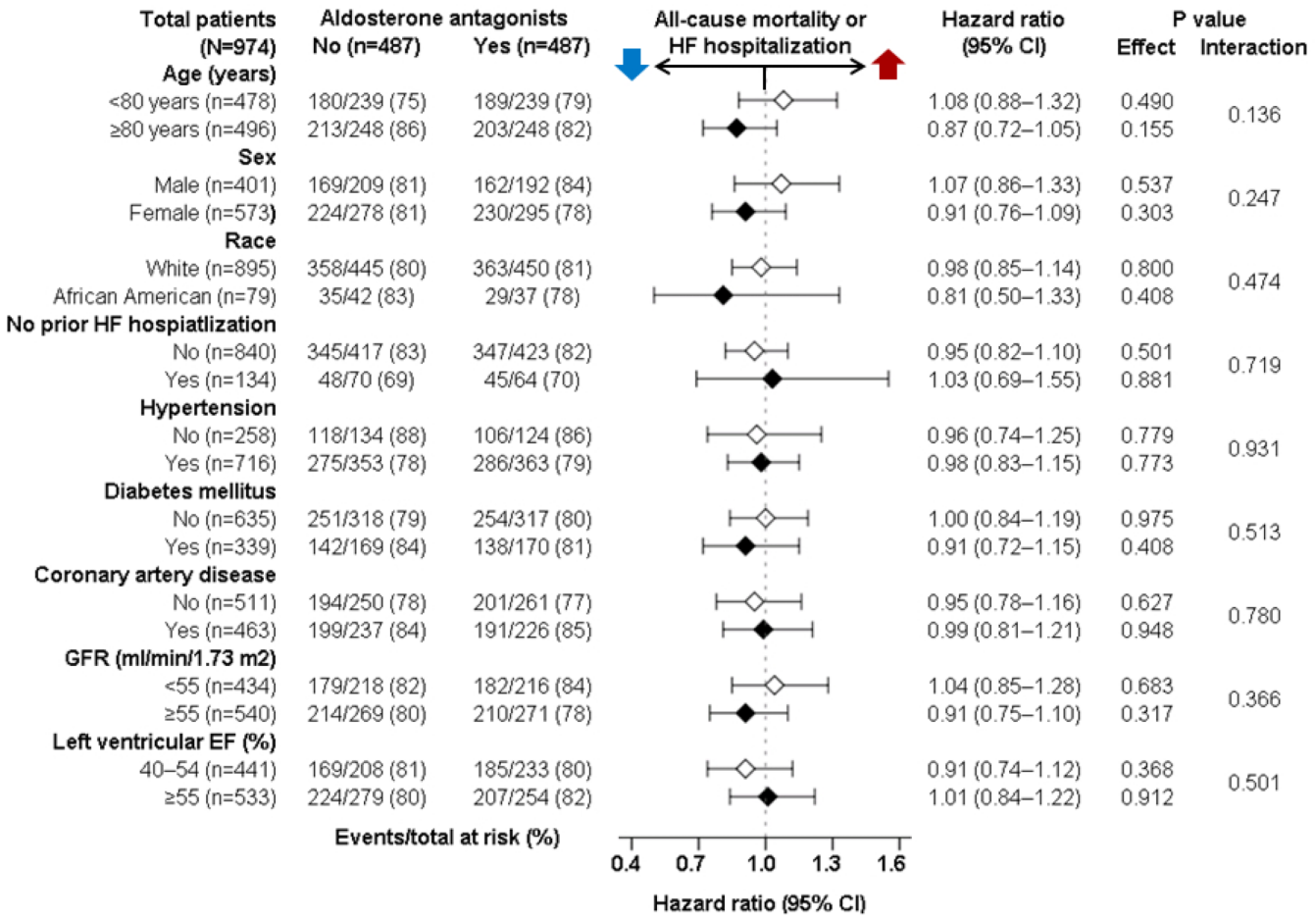

Figure 3. Subgroup analysis for primary composite endpoint

Association of new discharge prescriptions for aldosterone antagonists with primary composite endpoint of all-cause mortality or HF hospitalization in subgroups of propensity-matched older HF-PEF patients (EF=ejection fraction, GFR=glomerular filtration rate, HF=heart failure)

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Table 1

Baseline characteristics of older patients with heart failure and preserved ejection fraction (HF-PEF), by new discharge prescription of aldosterone antagonists, before and after propensity score matching

Variables Mean (±SD) or n (%)	Before propensity score matching			After propensity score matching		
	Aldosterone antagonists		P value	Aldosterone antagonists		P value
	No (n=7521)	Yes (n=492)		No (n=487)	Yes (n=487)	
Age (years)	81 (±8)	80 (±7)	0.094	80 (±7)	80 (±7)	0.839
Female	4754 (63)	297 (60)	0.206	278 (57)	295 (61)	0.288
African American	681 (9)	37 (8)	0.248	42 (9)	37 (8)	0.630
Left ventricular ejection fraction (%)	55 (±9)	54 (±10)	<0.001	54 (±9)	54 (±10)	0.812
Past medical history						
No prior heart failure hospitalization	1139 (15)	64 (13)	0.199	70 (14)	64 (13)	0.643
Coronary artery disease	3453 (46)	229 (47)	0.785	237 (49)	226 (46)	0.526
Hypertension	5618 (75)	366 (74)	0.879	353 (73)	363 (75)	0.505
Diabetes mellitus	2764 (37)	172 (35)	0.424	169 (35)	170 (35)	1.000
Atrial fibrillation	2865 (38)	227 (46)	<0.001	219 (45)	223 (46)	0.845
Ventricular arrhythmia	175 (2)	27 (5)	<0.001	23 (5)	25 (5)	0.878
Peripheral vascular disease	977 (13)	78 (16)	0.069	65 (13)	76 (16)	0.351
Chronic kidney disease	4423 (59)	270 (55)	0.086	267 (55)	267 (55)	1.000
Depression	849 (11)	75 (15)	0.008	72 (15)	74 (15)	0.925
Admission clinical presentation						
Dyspnea on exertion	4707 (63)	334 (68)	0.018	338 (69)	330 (68)	0.622
Orthopnea	1812 (24)	143 (29)	0.013	131 (27)	140 (29)	0.571
Paroxysmal nocturnal dyspnea	963 (13)	89 (18)	0.001	88 (18)	85 (18)	0.866
Dyspnea at rest	3300 (44)	221 (45)	0.652	221 (45)	218 (45)	0.901
Chest pain	1652 (22)	89 (18)	0.043	74 (15)	88 (18)	0.258
Pulse (beats per minute)	85 (±21)	83 (±20)	0.133	83 (±19)	83 (±20)	0.916
Systolic blood pressure (mmHg)	149 (±31)	146 (±30)	0.061	146 (±30)	146 (±29)	0.657
Diastolic blood pressure (mmHg)	75 (±18)	75 (±19)	0.917	75 (±18)	75 (±19)	0.450
Jugular venous pressure elevation	1935 (26)	149 (30)	0.026	151 (31)	148 (30)	0.888
Pulmonary râles	4828 (64)	350 (71)	0.002	339 (70)	346 (71)	0.659

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Variables Mean (±SD) or n (%)	Before propensity score matching			After propensity score matching		
	Aldosterone antagonists		P value	Aldosterone antagonists		P value
	No (n=7521)	Yes (n=492)		No (n=487)	Yes (n=487)	
Lower extremity edema	4882 (65)	369 (75)	<0.001	369 (76)	365 (75)	0.813
Admission laboratory values						
Serum creatinine (mg/dL)	1.2 (±0.4)	1.2 (±0.4)	0.252	1.2 (±0.4)	1.2 (±0.4)	0.446
Serum brain natriuretic peptide (pg/mL)	871 (±780)	906 (±751)	0.343	895 (±704)	908 (±754)	0.780
Serum troponin elevation *	1068 (14)	86 (18)	0.045	81 (17)	86 (18)	0.733
Length of hospital stay	8 (±169)	6 (±5)	0.826	6 (±5)	6 (±5)	0.614
Hospital characteristics						
Interventional	5652 (75)	387 (79)	0.080	392 (81)	382 (78)	0.477
Transplant	985 (13)	48 (10)	0.032	62 (13)	48 (10)	0.161
Hospital location by region						
Midwest	2338 (31)	117 (24)		119 (24)	117 (24)	
Northeast	1345 (18)	87 (18)	0.004	84 (17)	87 (18)	0.322
South	2355 (31)	178 (36)		169 (35)	175 (36)	
West	1483 (20)	110 (22)		115 (24)	108 (22)	
In-hospital treatment/procedure						
Dobutamine	93 (1)	14 (3)	0.003	16 (3)	13 (3)	0.690
Nesiritide	480 (6)	64 (13)	<0.001	68 (14)	60 (12)	0.451
Discharge medication						
Angiotensin-converting enzyme inhibitors	3656 (49)	267 (54)	0.015	254 (52)	265 (54)	0.512
Angiotensin receptors blockers	972 (13)	77 (16)	0.082	80 (16)	75 (15)	0.735
Beta-blockers	4402 (59)	343 (70)	<0.001	348 (72)	338 (69)	0.502
Diuretics	6206 (83)	439 (89)	<0.001	431 (89)	434 (89)	0.832
Digoxin	1678 (22)	147 (30)	<0.001	143 (29)	144 (30)	1.000
Nitrates	1809 (24)	134 (27)	0.110	132 (27)	132 (27)	1.000
Warfarin	2035 (27)	188 (38)	<0.001	173 (36)	185 (38)	0.441
Anti-platelet drugs	1080 (14)	61 (12)	0.228	59 (12)	60 (12)	1.000
Aspirin	3504 (47)	226 (46)	0.778	227 (47)	224 (46)	0.900
Statins	2345 (31)	172 (35)	0.080	177 (36)	170 (35)	0.693

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* Determined by local laboratories

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Table 2

Association of discharge prescriptions for aldosterone antagonists with outcomes in propensity-matched inception cohort of older patients with heart failure and preserved ejection fraction (HF-PEF)

Outcomes	Events (%)		Absolute risk difference*	Hazard ratio† (95% CI)	P value
	Aldosterone antagonists				
New prescription	**No (n=487)**	**Yes (n=487)**			
All-cause mortality or HF hospitalization	393 (81%)	392 (81%)	0%	0.97 (0.84–1.11)	0.628
All-cause mortality	328 (67%)	335 (69%)	+2%	1.03 (0.89–1.20)	0.693
HF hospitalization	219 (45%)	199 (41%)	−4%	0.88 (0.73–1.07)	0.188
All-cause hospitalization	416 (85%)	446 (92%)	+7%	1.10 (0.96–1.26)	0.156
Any (new or continuation) prescription	**No (n=712)**	**Yes (n=712)**			
All-cause mortality or HF hospitalization	583 (82%)	587 (82%)	0%	1.00 (0.89–1.12)	0.991
All-cause mortality	502 (71%)	492 (69%)	−2%	0.94 (0.83–1.07)	0.358
HF hospitalization	327 (46%)	326 (46%)	0%	0.99 (0.85–1.16)	0.918
All-cause hospitalization	616 (87%)	639 (90%)	+3%	1.06 (0.94–1.18)	0.343

*Absolute risk differences were calculated by subtracting percent events in patients not receiving aldosterone antagonists from those receiving those drugs

†Hazard ratios comparing patients receiving aldosterone antagonists versus those not receiving those drugs