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

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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 (≥65 years of age) HF-PEF (EF ≥40%) patients in the Medicare-linked OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) trial, 8,013 patients had no prior aldosterone antagonist use and no current contraindications; 492 (6% of these 8,013) patients received new prescriptions for aldosterone antagonists. We assembled a matched cohort of 487 pairs of patients receiving and not receiving aldosterone antagonists, who had a similar propensity to receive these drugs and were balanced on 116 baseline characteristics.

Results Patients had a mean age of 80 years old, 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 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 to 1.11; p = 0.628). Aldosterone antagonists had no association with all-cause mortality (HR: 1.03; 95% CI: 0.89 to 1.20; p = 0.693) or HF hospitalization (HR: 0.88; 95% CI: 0.73 to 1.07; p = 0.188). Among 8013 prematched patients, multivariable-adjusted HR for the primary composite endpoint associated with aldosterone antagonist use was 0.93 (95% CI: 0.83 to 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. (J Am Coll Cardiol HF 2013;1:40–7)

Aldosterone antagonists have been shown to reduce the risk of mortality and hospitalization in heart failure (HF) and reduced ejection fraction (REF) (1–3). HF and preserved ejection fraction (PEF) comprise nearly half of all HF patients and have a prognosis similar to patients with 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

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ventricular hypertrophy, renal fibrosis, and vascular injury, this may be a key therapeutic target in these patients (6). Furthermore, these drugs have been shown to reduce myocardial fibrosis and improve diastolic function in HF-PEF (7,8). However, the role of aldosterone antagonists in 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 studied in the ongoing multicenter, randomized, double-blind, placebo-controlled TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) 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). Furthermore, 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.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ARBs = angiotensin receptors blockers
CI = confidence interval
HF-PEF = heart failure and preserved ejection fraction
HF-REF = heart failure and reduced ejection fraction
HR = hazard ratio
RCT = randomized clinical trial

Methods

Data sources and study population. The OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) database is a national registry of hospitalized HF patients, 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 from March 2003 to 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 an EF of 40% to 50% are characteristically and prognostically similar to those with an EF >50% (5), we used an EF of ≥40% to define HF-PEF, and of 48,612 HF hospitalizations, 20,839 occurred in those with HF-PEF. To obtain long-term outcome data, we linked OPTIMIZE-HF to Medicare claims data consisting of 100% Medicare Provider Analysis and Review (MedPAR) file and 100% 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 of age, and 10,570 were discharged alive (13).

Assembly of an eligible cohort. Data for admission and discharge use of aldosterone antagonists and other key HF medications were collected by chart abstraction. Except for beta-blockers, data for individual drugs and dosages were not available for other drugs including aldosterone antagonists. To assemble a cohort eligible for aldosterone antagonist therapy, we excluded patients who had contraindications to the use of these drugs. As such, patients with impaired renal function, defined as serum creatinine concentration of >2.5 mg/dl in males and >2.0 mg/dl in females (n = 1,443), and an estimated glomerular filtration rate (eGFR) of <30 ml/min/1.73 m^2 (n = 602) were excluded (17). In addition, 193 patients receiving both angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) agents were excluded (18). Because data for admission serum potassium were unavailable, we also excluded 91 patients whose preadmission aldosterone antagonist therapy was discontinued before hospital discharge. Thus, after excluding a total of 2,329 patients with potential contraindications and intolerance, the remaining 8,241 patients were considered eligible for discharge aldosterone antagonist therapy.

Assembly of an inception cohort. Because receipt of study drug prior to study baseline may affect baseline characteristics and may also cause 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 8,013 hospitalized patients not receiving aldosterone antagonists, and, of these patients, 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 those not receiving a new discharge prescription for aldosterone antagonists (Table 1, Fig. 1), we used propensity scores for the receipt of aldosterone antagonists to assemble a cohort in whom the two treatment groups would be balanced on all measured baseline characteristics (22–24). We estimated propensity scores for each of the 8,013 patients using a nonparsimonious multivariable logistic regression model, in which 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 492 patients receiving aldosterone antagonists with another 487 patients not receiving these drugs but who 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 postmatch 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

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Table 1 Baseline Characteristics of Older Patients With HF-PEF by New Discharge Prescription of Aldosterone Antagonists Before and After Propensity Score Matching

	Before Propensity Score Matching			After Propensity Score Matching		
	Aldosterone Antagonists			Aldosterone Antagonists		
Variables	No (n = 7521)	Yes (n = 492)	p Value	No (n = 487)	Yes (n = 487)	p Value
Age (yrs)	81 ± 8	80 ± 7	0.094	80 ± 7	80 ± 7	0.839
Female	4,754 (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
Medical history						
No prior heart failure hospitalization	1,139 (15)	64 (13)	0.199	70 (14)	64 (13)	0.643
Coronary artery disease	3,453 (46)	229 (47)	0.785	237 (49)	226 (46)	0.526
Hypertension	5,618 (75)	366 (74)	0.879	353 (73)	363 (75)	0.505
Diabetes mellitus	2,764 (37)	172 (35)	0.424	169 (35)	170 (35)	1.000
Atrial fibrillation	2,865 (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	4,423 (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	4,707 (63)	334 (68)	0.018	338 (69)	330 (68)	0.622
Orthopnea	1,812 (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	3,300 (44)	221 (45)	0.652	221 (45)	218 (45)	0.901
Chest pain	1,652 (22)	89 (18)	0.043	74 (15)	88 (18)	0.258
Pulse (beats per min)	85 ± 21	83 ± 20	0.133	83 ± 19	83 ± 20	0.916
Systolic blood pressure (mm Hg)	149 ± 31	146 ± 30	0.061	146 ± 30	146 ± 29	0.657
Diastolic blood pressure (mm Hg)	75 ± 18	75 ± 19	0.917	75 ± 18	75 ± 19	0.450
Jugular venous pressure elevation	1,935 (26)	149 (30)	0.026	151 (31)	148 (30)	0.888
Pulmonary râles	4,828 (64)	350 (71)	0.002	339 (70)	346 (71)	0.659
Lower extremity edema	4,882 (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*	1,068 (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	5,652 (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	2,338 (31)	117 (24)	0.004	119 (24)	117 (24)	0.322
Northeast	1,345 (18)	87 (18)		84 (17)	87 (18)	
South	2,355 (31)	178 (36)		169 (35)	175 (36)	
West	1,483 (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	3,656 (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	4,402 (59)	343 (70)	<0.001	348 (72)	338 (69)	0.502
Diuretic agents	6,206 (83)	439 (89)	<0.001	431 (89)	434 (89)	0.832
Digoxin	1,678 (22)	147 (30)	<0.001	143 (29)	144 (30)	1.000
Nitrates	1,809 (24)	134 (27)	0.110	132 (27)	132 (27)	1.000
Warfarin	2,035 (27)	188 (38)	<0.001	173 (36)	185 (38)	0.441
Antiplatelet drugs	1,080 (14)	61 (12)	0.228	59 (12)	60 (12)	1.000
Aspirin	3,504 (47)	226 (46)	0.778	227 (47)	224 (46)	0.900
Statin agents	2,345 (31)	172 (35)	0.080	177 (36)	170 (35)	0.693

Values are mean ± SD or n (%). *Determined by local laboratories.

HF-PEF = heart failure and preserved ejection fraction.

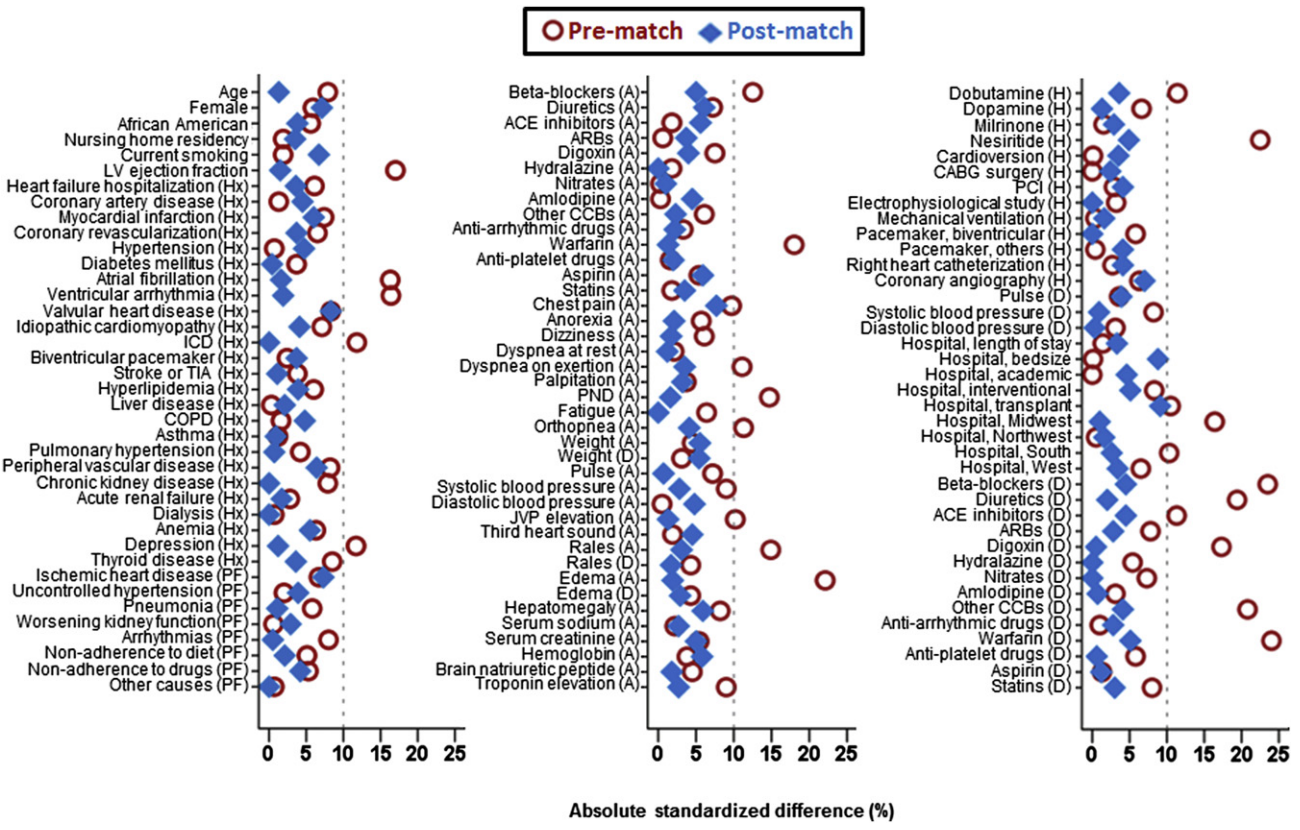

Figure 1 **Love Plot for Absolute Standardized Differences**

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 = 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. (*The 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.)

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).

We replicated the above-described process to assemble a second balanced propensity-matched cohort in which HF-PEF was defined as an EF of ≥50%. Finally, to determine clinical effectiveness of any (new or continuation) discharge prescription of aldosterone antagonists, we repeated the above process in 8,241 patients eligible for aldosterone antagonist therapy, of whom 720 (9%) received discharge prescriptions to initiate or continue their aldosterone antagonist regimens. 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 approximately 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 outcome 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 the Pearson's Chi-square and Wilcoxon rank-sum tests for prematch and McNemar test and paired sample *t* test for postmatch 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 primary endpoint, we conducted subgroup analyses. A formal sensitivity analysis was conducted to estimate the degree of hidden bias that could potentially explain a significant association among matched patients (33). We repeated our analyses in the prematched cohort, using three

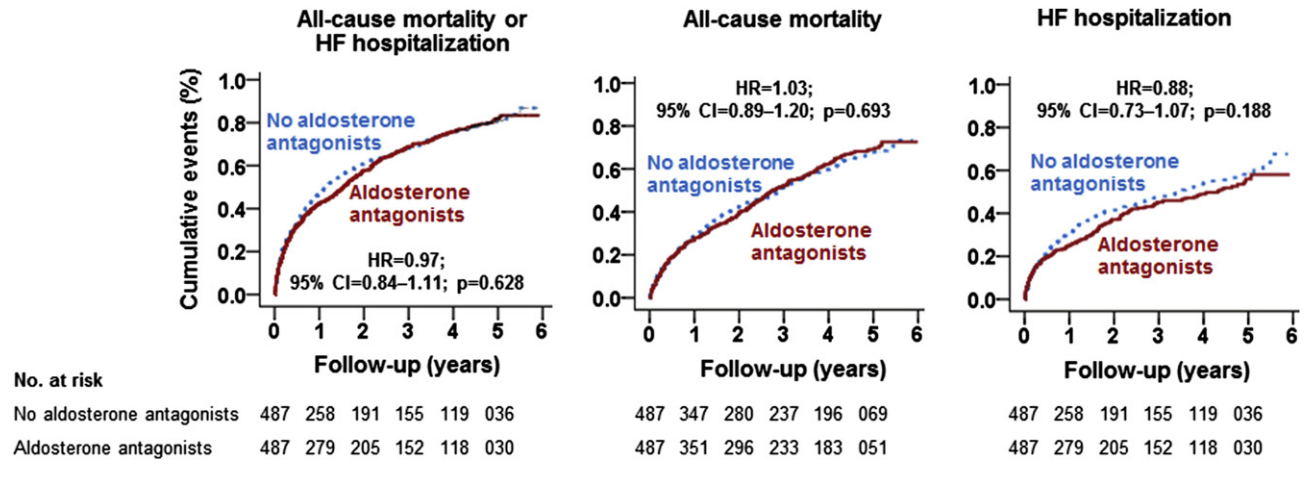

Figure 2 Kaplan-Meier Plots of Outcomes

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.

different approaches: 1) unadjusted; 2) multivariable-adjusted, using all 116 baseline characteristics; and 3) propensity score-adjusted. All statistical tests were 2-tailed with a p value of <0.05 considered significant. SPSS for Windows version 20 (Release 2011, IBM Corp. Armonk, New York) was used for data analysis.

Results

Baseline characteristics. Matched patients (n = 974) had a mean age of 80 ± 7 years and a mean left ventricular ejection fraction (LVEF) of 54 ± 9%; 59% were women, and 8% were African American. Patients receiving aldosterone antagonists had lower mean LVEF and a higher symptom burden and were more likely to receive other neurohormonal antagonists, but no differences were found in blood pressure or serum creatinine levels (Table 1, Fig. 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) 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 to 1.11; p = 0.628) (Fig. 2, Table 2). This association was homogeneous across various clinically relevant subgroups of patients (Fig. 3). Similar association was observed when the Cox model was stratified by matching (HR: 0.93; 95% CI: 0.78 to 1.12; p = 0.933). There was no significant association with the primary composite endpoint at the end of the first and second years 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 an EF value of >50% was used to define HF-PEF.

Among the 8,013 prematched patients, the primary composite endpoint occurred in 81% (397 of 492) and 82% (6,126 of 7,521) 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 to 1.07; p = 0.452). Corresponding multivariable-adjusted and propensity score-adjusted HRs were 0.93 (95% CI: 0.83 to 1.03; p = 0.144) and 0.95 (95% CI: 0.86 to 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 of 712) of patients receiving any (new or continuation) discharge prescription for aldosterone antagonists versus 82% (583 of 712) of patients not receiving any aldosterone antagonists (HR associated with aldosterone antagonists use, 1.00; 95% CI: 0.89 to 1.12; p = 0.991) (Table 2). Among the 8,241 prematched patients, unadjusted, multivariable-adjusted, and propensity score-adjusted HRs for the primary composite endpoint associated with any (new or continuation) use of aldosterone antagonists were 1.04 (95% CI: 0.96 to 1.14; p = 0.311), 0.97 (95% CI: 0.89 to 1.06; p = 0.492), and 0.98 (95% CI: 0.90 to 1.07; p = 0.609), respectively. A discharge prescription for aldosterone antagonists (new or continuation) had no significant

Table 2 Association of Discharge Prescriptions for Aldosterone Antagonists With Outcomes in Propensity-Matched Inception Cohort of Older Patients With 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 the percentage of events in patients not receiving aldosterone antagonists from those in patients receiving those drugs. †Hazard ratios comparing patients receiving aldosterone antagonists versus those not receiving those drugs.

association with all-cause mortality or hospitalization among matched patients (Table 2). Similar associations were observed in patients in whom we used an EF value of >50% to define HF-PEF.

Discussion

Findings from the current analysis demonstrated 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 more than 100 potential baseline characteristics and more than 80% of whom experienced a primary endpoint event during 6 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 about the role of

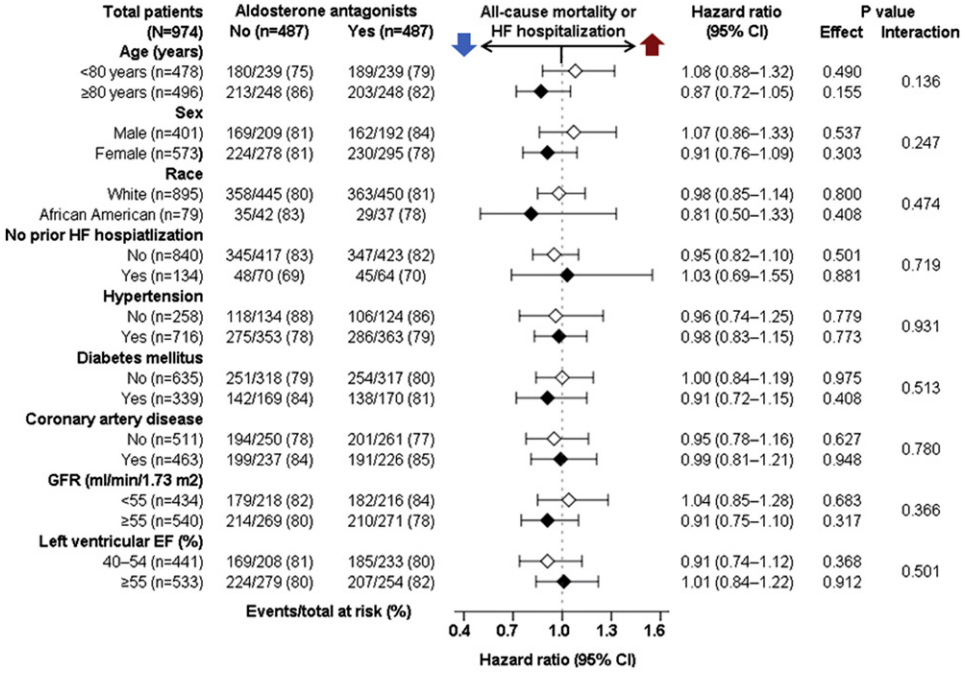

Figure 3 Subgroup Analysis for Primary Composite Endpoint

Association of new discharge prescriptions for aldosterone antagonists with the 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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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 is 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 their effects in HF-REF, these drugs may not improve clinical outcomes in HF-PEF. This is intriguing, as in the RALES (Randomized Aldactone Evaluation Study), spironolactone significantly reduced both total mortality and HF hospitalization in cases of HF-REF (1) and significantly reduced the composite endpoint of total mortality or HF hospitalization in HF-REF in the EMPHASIS (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) (3). Although the OPTIMIZE-HF registry did not collect data on individual aldosterone antagonists, a post-hoc analysis of a similar cohort suggests that spironolactone was the most common aldosterone antagonists during the study period (35). Furthermore, 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 prematched cohort is also intriguing and 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 be 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 for 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 are 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 on 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).

Study 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. 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 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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