

Associations Between Aldosterone Antagonist Therapy and Risks of Mortality and Readmission Among Patients With Heart Failure and Reduced Ejection Fraction

Adrian F. Hernandez, MD, MHS

Xiaojuan Mi, PhD

Bradley G. Hammill, MS

Stephen C. Hammill, MD

Paul A. Heidenreich, MD

Frederick A. Masoudi, MD, MSPH

Laura G. Qualls, MS

Eric D. Peterson, MD, MPH

Gregg C. Fonarow, MD

Lesley H. Curtis, PhD

DURING THE PAST 30 YEARS, large randomized trials have established the efficacy of multiple therapies for reducing mortality among patients with heart failure and reduced ejection fraction.¹ Among the most efficacious therapies for heart failure are the aldosterone antagonists spironolactone and eplerenone. In 2 landmark trials, these agents reduced mortality by 24% to 30% and readmission for heart failure by nearly 40%.^{2,3} Despite these findings and subsequent class I guideline recommendations, the use of aldosterone antagonist therapy remains lower than expected.^{1,4,5}

Slow and varied adoption of aldosterone antagonists in clinical practice may be due, in part, to uncertainty about their effectiveness and safety outside clinical trials.⁶ This uncertainty is especially relevant for patients at high risk

See also pp 2108 and 2144.

Context Aldosterone antagonist therapy for heart failure and reduced ejection fraction has been highly efficacious in randomized trials. However, questions remain regarding the effectiveness and safety of the therapy in clinical practice.

Objective To examine the clinical effectiveness of newly initiated aldosterone antagonist therapy among older patients hospitalized with heart failure and reduced ejection fraction.

Design, Setting, and Participants Using clinical registry data linked to Medicare claims from 2005 through 2010, we examined outcomes of eligible patients hospitalized with heart failure and reduced ejection fraction. We used Cox proportional hazards models and inverse-weighted estimates of the probability of treatment to adjust for treatment selection bias.

Main Outcome Measures All-cause mortality, cardiovascular readmission, and heart failure readmission at 3 years, and hyperkalemia readmission at 30 days and 1 year.

Results Among 5887 patients who met the inclusion criteria, the mean age was 77.6 years; of those 1070 (18.2%) started aldosterone antagonist therapy at discharge. Cumulative incidence rates among treated and untreated patients were 49.9% vs 51.2% ($P=.62$) for mortality; 63.8% vs 63.9% ($P=.65$) for cardiovascular readmission; and 38.7% vs 44.9% ($P<.001$) for heart failure readmission at 3 years; and 2.9% vs 1.2% ($P<.001$) for hyperkalemia readmission within 30 days and 8.9% vs 6.3% ($P=.002$) within 1 year. After inverse weighting for the probability of treatment, there were no significant differences in mortality (hazard ratio [HR], 1.04; 95% CI, 0.96-1.14; $P=.32$) and cardiovascular readmission (HR, 1.00; 95% CI, 0.91-1.09; $P=.94$). Heart failure readmission was lower among treated patients at 3 years (HR, 0.87; 95% CI, 0.77-0.98; $P=.02$). Readmission associated with hyperkalemia was higher with aldosterone antagonist therapy at 30 days (HR, 2.54; 95% CI, 1.51-4.29; $P<.001$) and 1 year (HR, 1.50; 95% CI, 1.23-1.84; $P<.001$).

Conclusions Initiation of aldosterone antagonist therapy at hospital discharge was not independently associated with improved mortality or cardiovascular readmission but was associated with improved heart failure readmission among eligible older patients with heart failure and reduced ejection fraction. There was a significant increase in the risk of readmission with hyperkalemia, predominantly within 30 days after discharge.

JAMA. 2012;308(20):2097-2107

www.jama.com

Author Affiliations: Duke Clinical Research Institute (Drs Hernandez, Mi, Peterson, and Curtis, Ms Qualls and Mr Hammill) and Department of Medicine (Drs Hernandez, Peterson, and Curtis), Duke University School of Medicine, Durham, North Carolina; Division of Cardiovascular Disease, Mayo Clinic, Rochester, Minnesota (Dr Hammill); VA Palo Alto Healthcare System, Palo Alto,

California (Dr Heidenreich); University of Colorado Anschutz Medical Campus, Aurora (Dr Masoudi); and Ahmanson-UCLA Cardiomyopathy Center, University of California, Los Angeles (Dr Fonarow).

Corresponding Author: Adrian F. Hernandez, MD, MHS, Duke Clinical Research Institute, PO Box 17969, Durham, NC 27715 (adrian.hernandez@duke.edu).

of hyperkalemia, such as older patients, patients with diabetes mellitus or chronic kidney disease, and patients using other renin-angiotensin-aldosterone system antagonists.⁷⁻⁹ High-risk patients, women, and patients in minority racial and ethnic groups are typically underrepresented in clinical trials, whereas patients who are generally adherent to therapy and follow-up tests are more likely to participate in trials.¹⁰

In response to questions about the effectiveness and safety of heart failure therapies in clinical practice, we designed the Comparative Effectiveness of Therapies for Heart Failure (COMPARE-HF) program using a national clinical registry linked to Medicare claims data to examine the clinical effectiveness of therapies such as aldosterone antagonists and associations with long-term outcomes of older patients discharged from a hospitalization for heart failure.¹¹

METHODS

Data Sources

Data for this study included clinical data from the American Heart Association's Get With the Guidelines-Heart Failure registry and Medicare claims data from the US Centers for Medicare & Medicaid Services. The registry is an ongoing web-based registry established to improve care for patients hospitalized with heart failure. It succeeded the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure registry. Details of the registry have been described previously.¹²

Patients are eligible if they are hospitalized with a primary diagnosis of heart failure or develop significant heart failure symptoms during a hospitalization for which heart failure was not the reason for admission. Heart failure diagnoses are identified with *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes 402.x1, 404.x1, 404.x3, and 428.x. The registry contains patient demographic characteristics, medical history, results of admission labora-

tory tests and examinations, contraindications for medications, and discharge medications. Outcome Sciences Inc (Cambridge, Massachusetts) is the data collection coordination center for the Get With the Guidelines-Heart Failure program. The Duke Clinical Research Institute serves as the data analysis center and has an agreement to analyze the aggregate deidentified data for research purposes.

The Medicare data include the 100% Medicare inpatient claims files and the corresponding denominator files for 2005 through 2010. The inpatient files contain institutional claims for facility costs covered under Medicare Part A and encrypted beneficiary identifiers, admission and discharge dates, dates of service, diagnosis related groups (DRGs), ICD-9-CM diagnosis and procedure codes, reimbursement amounts, hospital providers, and beneficiary demographic information. The denominator files include encrypted beneficiary identifiers, dates of birth, sex, race/ethnicity, dates of death, and information about program eligibility and enrollment.

We linked the registry data to the claims data using indirect identifiers—hospital identifier, admission date, discharge date, sex, and either birth date or month and year of birth.¹³ Combinations of these identifiers are almost always unique, enabling the identification of registry hospitalizations in Medicare claims. For patients with multiple hospitalizations in the registry, we selected the first hospitalization for the analysis. After linking the data, we used Medicare beneficiary identifiers to obtain subsequent events for beneficiaries with eligible hospitalizations.

The institutional review board of the Duke University Health System approved the study.

Study Cohort

In the linked data set, we identified patients 65 years or older who were discharged alive between January 1, 2005, and December 31, 2009, and were enrolled in fee-for-service Medicare. Consistent with guideline recommenda-

tions,¹ we required that patients were discharged home and had a documented history of heart failure before the index hospitalization. We also required patients to be eligible for aldosterone antagonist therapy, which we defined on the basis of registry documentation of left ventricular ejection fraction of 35% or less or a qualitative description of moderate or severe left ventricular systolic dysfunction; serum creatinine level at admission of 2.5 mg/dL or less in men and 2.0 mg/dL or less (to convert to micromoles per liter, multiply by 88.4) in women; and no documented contraindications to therapy. We did not include serum potassium level in the eligibility criteria, unless hyperkalemia was a documented contraindication to aldosterone antagonist use, because potassium levels were not collected in the registry until 2008. To minimize bias, we further required that patients had not previously received aldosterone antagonist therapy before the index hospitalization.¹⁴ We defined the date of cohort entry as the date of discharge from the index hospitalization.

Treatment

The treatment of interest was aldosterone antagonist therapy prescribed at discharge, as recorded in the registry. The treated group included all patients who received the prescription at discharge from the index hospitalization; the untreated group included all other patients in the study population.

Outcomes

The outcomes of interest were all-cause mortality, cardiovascular readmission, and heart failure readmission at 3 years and hyperkalemia readmission at 30 days and 1 year. We determined all-cause mortality on the basis of death dates in the Medicare denominator files, and we determined readmission on the basis of Medicare inpatient claims. We defined cardiovascular readmission using DRGs 104-112, 115-118, 121-145, 479, 514-518, 525-527, 535, 536, and 547-558 be-

fore October 1, 2007, and codes 215-238, 242-254, 258-262, and 280-316 on or after October 1, 2007.¹⁵ We defined heart failure readmission using DRG 127 before October 1, 2007, and 291-293 on or after October 1, 2007. We defined readmission for hyperkalemia using ICD-9-CM diagnosis code 276.7 in the primary position on an inpatient claim as the primary outcome and in any position as the secondary outcome. In post hoc analyses, we further categorized the reasons for cardiovascular readmissions as heart failure (DRG 127 before October 1, 2007, and 291-293 on or after October 1, 2007), elective or nonelective admission for an arrhythmia control device (DRGs 116-118, 514, 515, 536, 551, 552 before October 1, 2007, and 224-227, 242-245, 258-262 on or after October 1, 2007), acute myocardial infarction (DRGs 115, 121-123, 516, 526, 535 before October 1, 2007, and 222, 223, 280-285 on or after October 1, 2007), arrhythmia (DRGs 138 and 139 before October 1, 2007, and 308-310 on or after October 1, 2007), and other.

The follow-up period for all events was 3 years after discharge from the index hospitalization; days to events were calculated from the date of discharge. For patients who did not experience an event, we defined a censoring date as the earliest of (1) 30 days, 1 year, or 3 years after discharge, depending on the outcome; (2) the end of the period for which data were available (December 31, 2010); or (3) the date on which the patient's data were no longer available because the patient enrolled in a Medicare managed care plan. For the readmission outcomes, we treated death as a competing risk.

Subgroups

Subgroups of interest included age, sex, race/ethnicity, etiology of heart failure, and the presence or absence of diabetes mellitus, use of digoxin, and B-type natriuretic peptide level, all of which we ascertained from the registry.

Covariates

Covariates from the registry data included demographic characteristics (ie,

age, sex, race/ethnicity); medical history (ie, anemia, atrial fibrillation, chronic obstructive pulmonary disease, depression, diabetes mellitus, heart failure with ischemic etiology, hyperlipidemia, hypertension, pacemaker, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, renal insufficiency, and smoking in the previous year); results of admission laboratory tests (ie, left ventricular ejection fraction, blood urea nitrogen, and serum creatinine); vital signs at admission (ie, heart rate, respiratory rate, and systolic blood pressure); and discharge medications (ie, angiotensin-converting enzyme [ACE] inhibitor, aldosterone antagonist, angiotensin II receptor blocker [ARB], β -blocker, digoxin, diuretic, lipid-lowering agent, and warfarin). From the Medicare claims, we used Hierarchical Condition Category (HCC) codes for the index admission to define protein-calorie malnutrition (code 21), dementia (codes 49-50), disability (ie, paraplegia, 68; spinal cord disorders/injuries, 69; hemiplegia/hemiparesis, 100; paralysis, 101; speech, language, cognitive, and perceptual deficits, 102; and amputation and complications, 177 and 178), major psychiatric disorders (codes 54, 55, and 56), and chronic liver disease (codes 25, 26, and 27).¹⁶

Statistical Analysis

We describe the baseline characteristics of the study population using frequencies with percentages for categorical variables and means with SDs for continuous variables. We tested for differences between treatment groups using χ^2 tests for categorical variables and *t* tests for continuous variables. In addition, we compared treatment groups using standardized differences, calculated as the difference in means or proportions divided by a pooled estimate of the SD.^{17,18} Compared with traditional significance testing, standardized differences are not as sensitive to sample size and are useful in identifying meaningful differences. Typically, a standardized difference greater than 0.1 is considered meaningful.¹⁷

To describe observed outcomes, we compared the unadjusted cumulative incidence of each outcome at 30 days, 1 year, or 3 years after discharge between treatment groups, depending on the outcome. For mortality, we used the Kaplan-Meier method to estimate cumulative incidence and log-rank tests to assess differences between groups. For the readmission outcomes, we estimated cumulative incidence using the cumulative incidence function, which accounts for the competing risk of mortality, and we used Gray tests to assess differences between groups.¹⁹

To address confounding by observed covariates, we used inverse probability of treatment weighting methods, a type of propensity score analysis. Weights are based on results from a treatment selection model, estimated using logistic regression with receipt of aldosterone antagonist therapy as the dependent variable and the baseline characteristics—age, sex, race/ethnicity, anemia, atrial fibrillation, cerebrovascular accident, chronic obstructive pulmonary disease, depression, diabetes mellitus, hyperlipidemia, hypertension, ischemic etiology, pacemaker, peripheral vascular disease, renal insufficiency, smoking in the past year, claims-based history at admission (chronic liver disease, dementia, disability, malnutrition, psychiatric disorder), heart rate, respiratory rate, systolic blood pressure, left ventricular ejection fraction, serum creatinine, and serum urea nitrogen—as independent variables. The weights for each patient were calculated as the inverse of the probability of receiving the treatment the patient actually received conditional on observed covariates.²⁰ After weighting, we assessed the balance of baseline characteristics between treatment groups using χ^2 tests for categorical variables and *t* tests for continuous variables and by calculating standard differences.¹⁸

To estimate the association of treatment with each outcome, we used 3 Cox proportional hazards models. First, we estimated the unadjusted associations

Table 1. Baseline Characteristics of the Study Population

Characteristic	Aldosterone Antagonist at Discharge, No. (%)		P Value	Standardized Difference ^a
	Yes (n = 1070)	No (n = 4817)		
Age, mean (SD), y	76.8 (7.4)	77.8 (7.6)	<.001	0.13
Age group, y				
65-79	681 (63.6)	2780 (57.7)	<.001	0.12
≥80	389 (36.4)	2037 (42.3)		
Sex				
Women	378 (35.3)	1723 (35.8)	.78	0.01
Men	692 (64.7)	3094 (64.2)		
Race				
Black	149 (13.9)	560 (11.6)	.10	0.07
White	857 (80.1)	3940 (81.8)		
Other/unknown	64 (6.0)	317 (6.6)		
Medical history				
Anemia	120 (11.2)	568 (11.8)	.60	0.02
Atrial fibrillation	355 (33.2)	1644 (34.1)	.55	0.02
Cerebrovascular accident or transient ischemic attack	149 (13.9)	709 (14.7)	.51	0.02
Chronic obstructive pulmonary disease	298 (27.9)	1252 (26.0)	.21	0.04
Depression	76 (7.1)	330 (6.9)	.77	0.01
Diabetes mellitus	426 (39.8)	1834 (38.1)	.29	0.04
Hyperlipidemia	490 (45.8)	2344 (48.7)	.09	0.06
Hypertension	760 (71.0)	3486 (72.4)	.38	0.03
Ischemic etiology of heart failure	760 (71.0)	3614 (75.0)	.007	0.09
Pacemaker	206 (19.3)	924 (19.2)	.96	0.00
Peripheral vascular disease	116 (10.8)	677 (14.1)	.005	0.10
Renal insufficiency	99 (9.3)	591 (12.3)	.006	0.10
Smoking in the previous year	150 (14.0)	551 (11.4)	.02	0.08
Claims-based history at admission				
Chronic liver disease	11 (1.0)	19 (0.4)	.009	0.08
Dementia	37 (3.5)	185 (3.8)	.55	0.02
Disability	16 (1.5)	65 (1.3)	.71	0.01
Malnutrition	18 (1.7)	69 (1.4)	.54	0.02
Psychiatric disorder		36 (0.7)	.75	0.01
Vital signs at admission				
Heart rate, mean (SD), beats/min	85.3 (19.1)	83.7 (19.4)	.02	0.08
Heart rate, beats/min				
<80	434 (40.6)	2181 (45.3)	.03	0.10
80-100	412 (38.5)	1718 (35.7)		
>100	224 (20.9)	918 (19.1)		
Respiratory rate, breaths/min				
<30	1012 (94.6)	4514 (93.7)	.28	0.04
≥30	58 (5.4)	303 (6.3)		
Blood pressure, mean (SD), mm Hg				
Systolic				
<110	135 (26.8)	136 (26.6)	.06	0.06
110-150	178 (16.6)	718 (14.9)		
150-200	607 (56.7)	2748 (57.0)		
>200	285 (26.6)	1351 (28.0)		
Tests at admission				
Left ventricular ejection fraction, mean (SD), %	24.6 (7.2)	26.3 (7.1)	<.001	0.24
≤25%	665 (62.1)	2512 (52.1)	<.001	0.20
>25%	405 (37.9)	2305 (47.9)		
Serum creatinine, mean (SD), mg/dL	1.26 (0.40)	1.35 (0.44)	<.001	0.20
<1.5	762 (71.2)	3056 (63.4)	<.001	0.20
1.5-2.0	245 (22.9)	1246 (25.9)		
>2.0	63 (5.9)	515 (10.7)		

(continued)

Table 1. Baseline Characteristics of the Study Population (continued)

Characteristic	Aldosterone Antagonist at Discharge, No. (%)		P Value	Standardized Difference ^a
	Yes (n = 1070)	No (n = 4817)		
Tests at admission (continued)				
Serum urea nitrogen, mg/dL				
<20	387 (36.2)	1492 (31.0)	.004	0.11
20-50	623 (58.2)	3042 (63.2)		
>50	60 (5.6)	283 (5.9)		
Medications at discharge				
ACE inhibitor	707 (66.1)	2903 (60.3)	<.001	0.12
ARB	212 (19.8)	834 (17.3)	.05	0.06
ACE inhibitor and/or ARB	901 (84.2)	3681 (76.4)	<.001	0.20
β-Blocker	941 (87.9)	4134 (85.8)	.07	0.06
Digoxin	421 (39.3)	1260 (26.2)	<.001	0.28
Diuretic	885 (82.7)	3751 (77.9)	<.001	0.12
Lipid-lowering agent	628 (58.7)	2931 (60.8)	.19	0.04
Warfarin	386 (36.1)	1628 (33.8)	.16	0.05

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; blank cells indicate fewer than 11 observations.

SI conversion factors: To convert creatinine from mg/dL to μmol/L, multiply by 88.4 and urea nitrogen from mg/dL to mmol/L, multiply by 0.357.

^aCalculated as the difference in means or proportions divided by a pooled estimate of the SD. A standardized difference greater than 0.1 is typically considered meaningful.

using models in which the treatment group was the only variable. Second, we applied the patient weights when modeling to estimate the inverse-weighted association between treatment and outcome. Again, treatment group was the only variable in the model. Finally, we estimated the weighted Cox model, additionally controlling for medical therapies at discharge—ACE inhibitor or ARB, β-blocker, and digoxin—because these medications were determined after treatment assignment. Significance tests and confidence intervals for estimates from all models were based on robust standard errors to account for the clustering of patients by hospital. For this analysis, we report hazard ratios and 95% CIs. We used $\alpha = .05$ to determine statistical significance, and all tests were 2-sided.

In addition to estimating overall treatment effects, we estimated the associations of aldosterone antagonist therapy in prespecified subgroups by adding a subgroup variable and an interaction term between the subgroup variable and the treatment indicator to the models. We assessed differences between subgroups by testing the significance of the interaction term. We estimated the treatment associations in each

Table 2. Cumulative Incidence of Mortality and Readmission

Outcome	Aldosterone Antagonist at Discharge, No. (Rate) ^a		P Value
	Yes (n = 1070)	No (n = 4817)	
All-cause mortality within 3 y, No. (%)	494 (49.9)	2243 (51.2)	.62
Cardiovascular readmission within 3 y, No. (%) ^b	662 (63.8)	2963 (63.9)	.65
Heart failure	316 (30.3)	1593 (34.1)	.02
Elective arrhythmia control device	68 (6.5)	199 (4.2)	.002
Nonelective arrhythmia control device	29 (2.8)	143 (3.1)	.63
Acute myocardial infarction	38 (3.7)	205 (4.5)	.26
Arrhythmia	53 (5.4)	175 (3.9)	.05
Other	158 (15.2)	648 (13.9)	.30
Heart failure readmission within 3 y, No. (%)	401 (38.7)	2062 (44.9)	<.001
Readmission, No. (%)			
Within 30 d with primary diagnosis of hyperkalemia ^c			.007
Within 30 d with any diagnosis of hyperkalemia	31 (2.9)	58 (1.2)	<.001
Within 1 y with primary diagnosis of hyperkalemia ^c		17 (0.4)	.07
Within 1 y with any diagnosis of hyperkalemia	95 (8.9)	303 (6.3)	.002

^aValues are expressed as number of events (cumulative incidence per 100 patients at risk).

^bSubcategorization of cardiovascular readmission refers to the first readmission.

^cEmpty cells indicates fewer than 11 observations.

subgroup using model contrasts. Because of the multiple comparisons in this analysis, we report 99% CIs and used $\alpha = .01$ to establish statistical significance. All tests were 2-sided.

Because the discharge prescription flag recorded in the Get With the Guidelines-Heart Failure registry was not a perfect measure of exposure to aldosterone antagonist therapy, we per-

formed a sensitivity analysis using Medicare prescription drug event data available for a subset of the study population. The analysis included patients discharged between January 1, 2006, and December 31, 2009, who were enrolled in Medicare Part D. We used a person-time approach to define treatment group.²¹ We defined the time between hospital discharge and the date of the first aldosterone antagonist pre-

scription as immortal person-time and classified it as unexposed. We classified subsequent follow-up time as exposed. We classified all other patients as unexposed.

We used SAS version 9.2 (SAS Institute Inc) for all analyses.

RESULTS

In the linked data set, we identified 40 744 patients 65 years or older who were discharged alive during the study period and were enrolled in fee-for-service Medicare. A total of 25 064 patients were discharged home with a documented history of heart failure; 7553 of these were eligible for aldosterone antagonist therapy, 5887 of whom had not been treated previously. Of the 5887

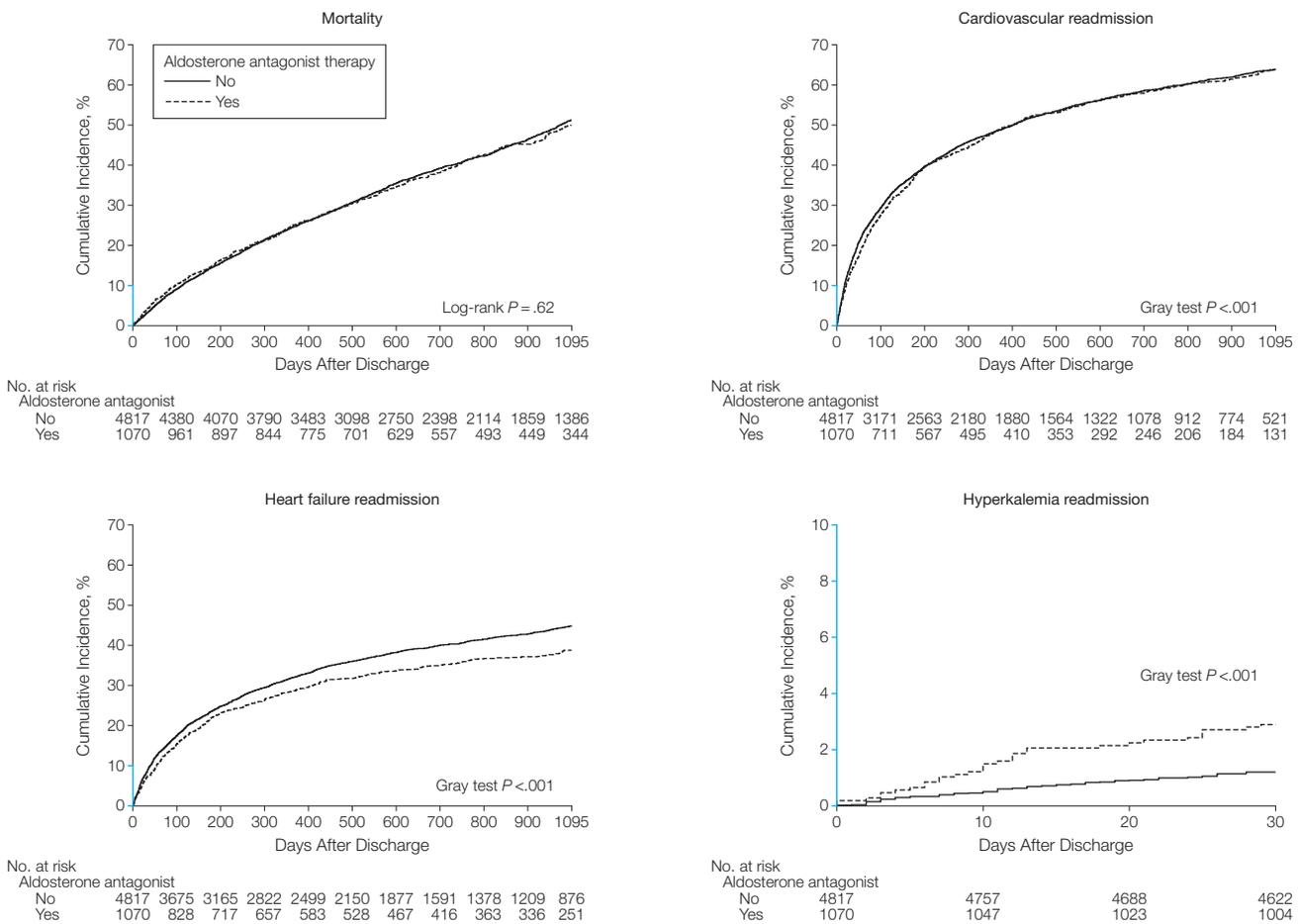
patients who met the inclusion criteria from 246 hospitals, 1070 received a prescription for an aldosterone antagonist at discharge. Compared with patients who did not meet the inclusion criteria, patients in the analysis cohort were younger (77.3 vs 80.3 years) and were more likely to be men (63.8% vs 41.3%) and to have ischemic heart failure (74.2% vs 59.5%; $P < .001$ for all comparisons).

TABLE 1 shows the baseline characteristics of the study population. Patients in the treated group were younger, had a lower degree of renal insufficiency, had lower left ventricular ejection fraction, and were more likely to receive digoxin and loop diuretics. Patients in the untreated group were more likely to have ischemic heart dis-

ease and were less likely to receive other evidence-based therapies for heart failure, such as ACE inhibitors or ARBs.

TABLE 2 and the FIGURE show the observed cumulative incidence of the study outcomes. Rates of all-cause mortality (49.9% vs 51.2%; $P = .62$) and cardiovascular readmission (63.8% vs 63.9%; $P = .65$) were similar between the treatment groups at 3 years. The cumulative incidence rates of arrhythmia (5.4% vs 3.9%; $P = .05$) and elective readmission for an arrhythmia control device (6.5% vs 4.2%; $P = .002$) were higher for the treated group. In contrast, the cumulative incidence of the first heart failure readmission was significantly lower in the treated group (38.7% vs 44.9%; $P < .001$). The hyperkalemia readmission rates at 30 days

Figure. Cumulative Incidence of Mortality, Cardiovascular Readmission, Heart Failure Readmission, and Hyperkalemia Readmission



The y-axis scale shown in blue indicates the range from 0% to 10%.

(2.9% vs 1.2%; $P < .001$) and 1 year (8.9% vs 6.3%; $P = .002$) were higher in the treated group; however, hyperkalemia was seldom the primary diagnosis for these readmissions, and the absolute increase in hyperkalemia as a primary diagnosis was small.

TABLE 3 shows the baseline characteristics of the study population after application of inverse probability weights. eTable 1, available at <http://www.jama.com>, shows the results of the treatment selection model. There were no significant differences between groups, except that patients in the treated group were more likely to be discharged with ACE inhibitors or ARBs, diuretics, and digoxin.

TABLE 4 shows the estimated associations between aldosterone antagonist therapy and the study outcomes. In the unadjusted analysis, treatment was associated with a lower hazard of heart failure readmission but a higher hazard of hyperkalemia readmission, arrhythmia readmission, and readmission for an elective arrhythmia control device. After inverse weighting for the probability of treatment, there were no significant differences in the hazards of all-cause mortality or cardiovascular readmission. However, the hazard of heart failure readmission was significantly lower in the treated group in the inverse probability-weighted analysis. Finally, readmission associated with hyperkalemia was higher with aldosterone antagonist therapy within 30 days after discharge (2.54; 95% CI, 1.51-4.29; $P < .001$) and within 1 year after discharge (1.50; 95% CI, 1.23-1.84; $P < .001$). The results were similar after further adjustment for prescription of other medications at discharge.

In subgroup analyses (eTable 2), patients older than 80 years in the aldosterone antagonist treatment group had a lower risk of death. For cardiovascular and heart failure readmission, there was a significantly lower adjusted risk in patients 80 years and older in the treated group. In the subgroup of patients treated with digoxin, there were trends toward aldosterone antagonist ef-

fectiveness for cardiovascular readmission; the interaction term between aldosterone antagonist therapy and digoxin was statistically significant. Otherwise, there were no significant subgroup interactions in the risk-adjusted results. In the sensitivity analysis among patients with a Medicare Part D claim (eTable 3), the results were similar to those in the primary analysis, but the CIs were wider because of the smaller sample size.

COMMENT

Ours is among the largest clinical effectiveness studies of aldosterone antagonist therapy in eligible older patients hospitalized with heart failure and reduced ejection fraction. Overall, we found no significant differences in mortality or cardiovascular readmission between treated and untreated patients after adjustment for propensity of use, risk factors, and use of other medications. However, we found a significantly lower risk for first readmission for heart failure among treated patients. Treated patients had a higher risk of readmission with hyperkalemia, primarily in the first few weeks after discharge from the index hospitalization.

Although the pivotal efficacy trials and a systematic review of randomized trials reported impressive benefits of aldosterone antagonist therapy, questions remain about how well those benefits translate into clinical practice.^{2,3,22} Observational comparative effectiveness research may have an important role in informing clinical decision making when gaps in evidence exist.²³ Patient populations, monitoring, and procedures in clinical trial settings differ from those in clinical practice settings, and understanding whether real-world effectiveness matches the efficacy demonstrated in clinical trials is an important element in a continuously learning health care system.¹⁰ In addition, there remains persistent exclusion of older patients and those with some comorbid conditions from clinical trials.²⁴ By using a large national registry of patients hospitalized with heart failure,

our analysis provides insight into the effectiveness of aldosterone antagonist therapy in clinical practice among older patients, many of whom have multiple comorbid conditions and are underrepresented in clinical trials.

Our study differs from the 3 pivotal efficacy trials of aldosterone antagonists in several ways.^{2,3,25} The study was observational and therefore is subject to confounding. The population was from a hospitalized cohort of patients who were significantly older and more likely to have renal impairment, diabetes mellitus, and other comorbid conditions. The clinical trials had rigorous follow-up to ensure adherence to medical therapy, as well as close ambulatory follow-up to detect hyperkalemia. In trials, patients and their physicians are encouraged to maintain adherence and nonstudy aldosterone use is discouraged. The general quality of the sites and treating physicians in the trials may have differed from those participating in our inclusive community registry. Despite these differences, the 3-year mortality rate of 51.0% that we observed is similar to the rate observed in the Randomized Aldactone Evaluation Study.³ However, the risk-adjusted effectiveness of aldosterone antagonist therapy in our study did not mirror the findings of the efficacy studies, with the exception of the higher risk of hyperkalemia.

A potential explanation for our findings is that aldosterone antagonists have limited effectiveness regarding mortality in real-world settings among older patients. One potential reason for limited effectiveness may be a lack of adherence to or persistence with therapy. However, an analysis of medication persistence in a similar cohort of patients enrolled in Medicare Part D found a comparatively high persistence rate (L.H.C., unpublished data, 2012). Another potential reason for limited effectiveness may be that aldosterone antagonists are less effective and less safe as dosed and monitored in clinical practice. Previous studies have suggested higher rates of hyperkalemia and renal insufficiency in clinical practice than

Table 3. Baseline Characteristics of the Study Population After Application of Inverse Probability Weights

Characteristic	Aldosterone Antagonist at Discharge, No. (%)		P Value	Standardized Difference ^a
	Yes (n = 1070)	No (n = 4817)		
Age, mean (SD), y	77.6 (7.5)	77.6 (7.6)	.86	0.01
Age group, y				
65-79	635 (59.5)	2828 (58.7)	.64	0.02
≥80	432 (40.5)	1989 (41.3)		
Sex				
Women	383 (35.9)	1720 (35.7)	.89	0.00
Men	684 (64.1)	3098 (64.3)		
Race				
Black	132 (12.3)	582 (12.1)	.94	0.01
White	864 (81.0)	3923 (81.4)		
Other/unknown	71 (6.7)	312 (6.5)		
Medical history				
Anemia	126 (11.8)	563 (11.7)	.94	0.00
Atrial fibrillation	363 (34.0)	1636 (34.0)	.98	0.00
Cerebrovascular accident or transient ischemic attack	155 (14.5)	702 (14.6)	.95	0.00
Chronic obstructive pulmonary disease	273 (25.6)	1266 (26.3)	.62	0.02
Depression	75 (7.0)	333 (6.9)	.88	0.00
Diabetes mellitus	414 (38.8)	1851 (38.4)	.79	0.01
Hyperlipidemia	509 (47.7)	2319 (48.1)	.81	0.01
Hypertension	774 (72.6)	3476 (72.2)	.79	0.01
Ischemic etiology	796 (74.6)	3580 (74.3)	.86	0.01
Pacemaker	209 (19.6)	926 (19.2)	.80	0.01
Peripheral vascular disease	142 (13.3)	649 (13.5)	.86	0.01
Renal insufficiency	121 (11.3)	565 (11.7)	.72	0.01
Smoking in the previous year	126 (11.8)	573 (11.9)	.93	0.00
Claims-based history at admission				
Chronic liver disease		24 (0.5)	.99	0.00
Dementia	40 (3.7)	181 (3.8)	.97	0.00
Disability	16 (1.5)	66 (1.4)	.72	0.01
Malnutrition	15 (1.4)	71 (1.5)	.78	0.01
Psychiatric disorder		35 (0.7)	.84	0.01
Vital signs at admission				
Heart rate, mean (SD), beats/min	83.9 (18.8)	84.0 (19.5)	.88	0.01
Heart rate, beats/min				
<80	478 (44.8)	2141 (44.4)	.97	0.01
80-100	386 (36.1)	1743 (36.2)		
>100	204 (19.1)	934 (19.4)		
Respiratory rate, breaths/min				
<30	1002 (94.0)	4522 (93.9)	.93	0.00
≥30	65 (6.0)	295 (6.1)		
Blood pressure, mean (SD), mm Hg	135 (26.9)	136 (26.6)	.58	0.02
Systolic				
<110	161 (15.1)	732 (15.2)	>.99	0.00
110-150	608 (57.0)	2746 (57.0)		
>150	298 (27.9)	1339 (27.8)		
Tests at admission				
Left ventricular ejection fraction, mean (SD), %	25.9 (7.0)	26.0 (7.2)	.70	0.01
≤25	585 (54.8)	2596 (53.9)	.59	0.02
>25	482 (45.2)	2221 (46.1)		
Serum creatinine, mean (SD), mg/dL	1.32 (0.43)	1.33 (0.43)	.20	0.04
<1.5	696 (65.2)	3124 (64.9)	.89	0.02
1.5-2.0	271 (25.4)	1220 (25.3)		
>2.0	99 (9.3)	472 (9.8)		

(continued)

in clinical trials.⁹ Moreover, many patients with heart failure who begin aldosterone antagonist therapy in clinical practice do not undergo monitoring consistent with guideline recommendations.¹ Excess risks associated with undetected hyperkalemia and worsened renal function may have offset the mortality benefit of aldosterone

antagonist therapy in our study population.

Alternative explanations for the differences between our observations and previous findings include unmeasured confounding, residual confounding, and selection bias. Guidelines only recommend aldosterone antagonist therapy for patients with moderate to severe heart

failure symptoms; therefore, there may have been treatment-selection bias for which we could not adequately adjust. Even after we applied inverse probability weights, treated patients were more likely than untreated patients to receive digoxin at discharge—another therapy that is differentially prescribed to patients with more severe heart failure.

Table 3. Baseline Characteristics of the Study Population After Application of Inverse Probability Weights (continued)

Characteristic	Aldosterone Antagonist at Discharge, No. (%)		P Value	Standardized Difference ^a
	Yes (n = 1070)	No (n = 4817)		
Tests at admission (continued)				
Serum urea nitrogen, mg/dL				
<20	347 (32.5)	1539 (31.9)	.90	0.02
20-50	660 (61.9)	2998 (62.2)		
>50	60 (5.6)	280 (5.8)		
Medications at discharge				
ACE inhibitor	691 (64.7)	2924 (60.7)	.01	0.08
ARB	211 (19.8)	829 (17.2)	.05	0.07
ACE inhibitor and/or ARB	883 (82.8)	3698 (76.8)	<.001	0.15
β-Blocker	932 (87.4)	4137 (85.9)	.20	0.04
Digoxin	401 (37.6)	1270 (26.4)	<.001	0.24
Diuretic	884 (82.9)	3744 (77.7)	<.001	0.13
Lipid-lowering agent	644 (60.3)	2919 (60.6)	.88	0.01
Warfarin	381 (35.7)	1627 (33.8)	.22	0.04

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; blank cells indicate fewer than 11 observations.

SI conversion factors: To convert creatinine from mg/dL to μmol/L, multiply by 88.4 and urea nitrogen from mg/dL to mmol/L, multiply by 0.357.

^aCalculated as the difference in means or proportions divided by a pooled estimate of the SD. A standardized difference greater than 0.1 is typically considered meaningful.

Table 4. Associations Between Aldosterone Antagonist Therapy and Study Outcomes

Outcome	Association With Aldosterone Antagonist Therapy ^a					
	Unadjusted		Inverse-Weighted		Inverse-Weighted and Adjusted ^b	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
All-cause mortality within 3 y	0.98 (0.90-1.06)	.58	1.04 (0.96-1.14)	.32	1.05 (0.97-1.15)	.23
Cardiovascular readmission within 3 y ^c	0.99 (0.91-1.08)	.90	1.00 (0.91-1.09)	.94	1.01 (0.92-1.11)	.83
Heart failure	0.87 (0.76-0.99)	.04	0.90 (0.78-1.02)	.10	0.91 (0.80-1.04)	.18
Elective arrhythmia control device	1.56 (1.11-2.20)	.01	1.42 (0.98-2.05)	.06	1.39 (0.96-2.00)	.08
Nonelective arrhythmia control device	0.91 (0.61-1.36)	.64	0.91 (0.60-1.36)	.64	0.89 (0.59-1.33)	.57
Acute myocardial	0.83 (0.59-1.15)	.26	0.90 (0.63-1.28)	.56	0.92 (0.65-1.32)	.67
Arrhythmia	1.36 (1.00-1.84)	.05	1.29 (0.93-1.81)	.13	1.31 (0.92-1.86)	.13
Other	1.10 (0.92-1.30)	.29	1.11 (0.93-1.33)	.25	1.12 (0.94-1.34)	.22
Heart failure readmission within 3 y	0.84 (0.75-0.94)	.002	0.87 (0.77-0.98)	.02	0.88 (0.78-0.99)	.04
Hyperkalemia readmission						
Primary diagnosis within 30 d	6.02 (1.57-23.09)	.009	5.61 (1.34-23.45)	.02	5.96 (1.31-27.15)	.02
Any diagnosis within 30 d	2.43 (1.46-4.05)	<.001	2.54 (1.51-4.29)	<.001	2.51 (1.45-4.34)	.001
Primary diagnosis within 1 y	2.14 (0.98-4.66)	.06	2.12 (0.95-4.74)	.07	2.10 (0.91-4.84)	.08
Any diagnosis within 1 y	1.44 (1.19-1.75)	<.001	1.50 (1.23-1.84)	<.001	1.48 (1.20-1.84)	<.001

Abbreviation: HR, hazard ratio.

^aFrom Cox proportional hazards models comparing aldosterone antagonist therapy at discharge with no aldosterone antagonist therapy at discharge.

^bAfter adjustment for prescription of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β-blocker, or digoxin.

^cSubcategorization of cardiovascular readmission refers to the first readmission.

Observational studies have produced mixed results regarding associations between aldosterone antagonist therapy and outcomes. An analysis of data from the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting found nonsignificant higher odds of mortality at 2 years with aldosterone antagonist therapy. A nested case-control analysis from the same registry found no difference in risk-adjusted mortality.^{26,27} In contrast, a study of 946 patients hospitalized in Japan with heart failure and reduced ejection fraction found a nearly 40% lower risk of mortality with aldosterone antagonist therapy.²⁸ A hospital-level analysis of Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure data linked to Medicare claims—which may have been better able to limit confounding—suggested a benefit with greater use of aldosterone antagonists at hospital discharge.²⁹ Each of these studies differed from our study in important ways with regard to study population or methodology.

Our findings highlight the importance of conducting clinical trials that can be easily generalized to real-world practice and in which the most vulnerable patient groups are well represented. In clinical practice, rigorous protocols for aldosterone antagonist therapy could be established to ensure appropriate patient selection, correct dosing, and early follow-up visits to screen for hyperkalemia. Periodic assessment for medication adherence is also important. Developing protocols and systems that encourage optimal use and monitoring of aldosterone antagonist therapy may help to ensure that the effectiveness of this therapy in clinical practice approaches the efficacy achieved in clinical trials.

Consistent with best-practice guidelines for comparative effectiveness research, our study included a priori specifications of objectives and design,^{30,31} and the study design underwent independent peer review.¹¹ Nevertheless, our study has some limitations. We could

not eliminate the possibility of selection bias and residual confounding.³² Several clinical variables that are likely to be associated with aldosterone antagonist use and clinical outcomes were not available, including New York Heart Association functional classification, symptom severity, degree of congestion, stability of renal function, and dosing of loop diuretics. We also could not account for socioeconomic status, educational level, and health literacy. The population consisted of older patients enrolled in fee-for-service Medicare, so the findings may not be generalizable to all patients with heart failure and reduced ejection fraction. Finally, the Get With the Guidelines-Heart Failure registry is a voluntary quality-improvement program and may not be representative of all hospitals.

CONCLUSIONS

In this study, initiation of aldosterone antagonist therapy at hospital discharge was not independently associated with improved mortality or cardiovascular readmission among eligible older patients with heart failure and reduced ejection fraction but was associated with a modest reduction in the risk of hospitalization for heart failure. There was a slight absolute increase in readmission with hyperkalemia as the primary diagnosis, and there was a significant increase in readmission risk with hyperkalemia as with any diagnosis early after hospital discharge. Strict protocols for careful monitoring and early follow-up after initiation of aldosterone antagonist therapy are needed. Additional research is needed to evaluate the clinical effectiveness of aldosterone antagonists in the broad population of patients with heart failure and to identify strategies to overcome disparities between findings of clinical efficacy and clinical effectiveness.

Author Contributions: Dr Hernandez had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: B. Hammill, S. Hammill, Masoudi, Peterson, Fonarow, Curtis, Hernandez.

Acquisition of data: Peterson, Fonarow, Curtis, Hernandez.

Analysis and interpretation of data: Mi, S. Hammill, Heidenreich, Masoudi, Qualls, Fonarow, Hernandez.

Drafting of the manuscript: Mi, S. Hammill, Peterson, Fonarow, Hernandez.

Critical revision of the manuscript for important intellectual content: B. Hammill, S. Hammill, Heidenreich, Masoudi, Qualls, Peterson, Fonarow, Curtis.

Statistical analysis: Mi, B. Hammill.

Obtained funding: Peterson, Fonarow, Curtis, Hernandez.

Administrative, technical, or material support: Qualls, Fonarow, Hernandez.

Study supervision: Fonarow, Curtis, Hernandez.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Hernandez reported receiving grant funding from Amylin Pharmaceutical and Johnson & Johnson; and receiving honoraria from AstraZeneca, Corthera, and sanofi-aventis. Dr Masoudi reported receiving salary support through his institution from the American College of Cardiology and the Oklahoma Foundation for Medical Quality; and receiving payment for editorial board service from the American Heart Association and the Massachusetts Medical Society. Dr Peterson reported receiving grant funding from Eli Lilly & Co and Johnson & Johnson. Dr Fonarow reported receiving grant funding and other research support from GlaxoSmithKline; receiving honoraria from Boston Scientific/Guidant, GlaxoSmithKline, Medtronic, Merck, Novartis, Pfizer, and St Jude Medical; and serving as a consultant for Amgen, Gambro, GlaxoSmithKline, Medtronic, Merck, Novartis, Pfizer, Relypsa, Scios, and St Jude Medical. Dr Fonarow holds the Eliot Corday Chair of Cardiovascular Medicine at UCLA and is also supported by the Ahmanson Foundation. Dr Curtis reported receiving grant funding from GlaxoSmithKline, Johnson & Johnson, and the National Heart, Lung, and Blood Institute. Drs Hernandez, Setoguchi, Peterson, and Curtis have made available online detailed listings of financial disclosures (<https://www.dcri.org/about-us/conflict-of-interest>).

Funding/Support: This study was funded under contract number HHS290200500321 (Duke University DEClDE Center) from the Agency for Healthcare Research and Quality, US Department of Health and Human Services, as part of the Developing Evidence to Inform Decisions about Effectiveness (DEClDE) program. Dr Peterson was supported in part by grant number U19HS021092 from the Agency for Healthcare Research and Quality. Get With the Guidelines-Heart Failure is provided by the American Heart Association; is currently supported in part by Medtronic, Ortho-McNeil, and the American Heart Association Pharmaceutical Roundtable; and had been funded through support from GlaxoSmithKline.

Role of the Sponsor: The Agency for Healthcare Research and Quality had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Disclaimer: The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the US Department of Health and Human Services. Dr Peterson, a contributing editor for *JAMA*, was not involved in the editorial review of or the decision to publish this article.

Online-Only Material: eTables 1 through 3 are available at <http://www.jama.com>.

Additional Contributions: Damon M. Seils, MA, Duke University, provided editorial assistance and prepared the manuscript. Mr Seils did not receive compensation for his assistance apart from his employment at the institution where the study was conducted.

REFERENCES

- Jessup M, Abraham WT, Casey DE, et al. ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119(14):1977-2016.
- Zannad F, McMurray JJ, Krum H, et al; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364(1):11-21.
- Pitt B, Zannad F, Remme WJ, et al; Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341(10):709-717.
- Albert NM, Yancy CW, Liang L, et al. Use of aldosterone antagonists in heart failure. *JAMA*. 2009;302(15):1658-1665.
- Fonarow GC, Yancy CW, Hernandez AF, Peterson ED, Spertus JA, Heidenreich PA. Potential impact of optimal implementation of evidence-based heart failure therapies on mortality. *Am Heart J*. 2011;161(6):1024-1030.e3.
- Ghali JK, Massie BM, Mann DL, Rich MW. Heart failure guidelines, performance measures, and the practice of medicine: mind the gap. *J Am Coll Cardiol*. 2010;56(25):2077-2080.
- Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004;351(6):543-551.
- Tamirisa KP, Aaronson KD, Koelling TM. Spironolactone-induced renal insufficiency and hyperkalemia in patients with heart failure. *Am Heart J*. 2004;148(6):971-978.
- Masoudi FA, Gross CP, Wang Y, et al. Adoption of spironolactone therapy for older patients with heart failure and left ventricular systolic dysfunction in the United States, 1998-2001. *Circulation*. 2005;112(1):39-47.
- Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med*. 2002;162(15):1682-1688.
- Curtis LH, Mi X, Qualls LG, et al. Design and rationale of a retrospective clinical effectiveness study of aldosterone antagonist therapy in patients with heart failure. *Am Heart J*. 2012;163(6):946-953.e1.
- Fonarow GC, Abraham WT, Albert NM, et al. Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF): rationale and design. *Am Heart J*. 2004;148(1):43-51.
- Hammill BG, Hernandez AF, Peterson ED, Fonarow GC, Schulman KA, Curtis LH. Linking inpatient clinical registry data to Medicare claims data using indirect identifiers. *Am Heart J*. 2009;157(6):995-1000.
- Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol*. 2003;158(9):915-920.
- Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med*. 2009;360(14):1418-1428.
- Krumholz HM, Wang Y, Mattern JA, et al. An administrative claims model suitable for profiling hospital performance based on 30-day mortality rates among patients with heart failure. *Circulation*. 2006;113(13):1693-1701.
- Mamdani M, Sykora K, Li P, et al. Reader's guide to critical appraisal of cohort studies, 2: assessing potential for confounding. *BMJ*. 2005;330(7497):960-962.
- Austin PC, Mamdani MM. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. *Stat Med*. 2006;25(12):2084-2106.
- Gray RJ. A class of K -sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988;16(3):1141-1154.
- Curtis LH, Hammill BG, Eisenstein EL, Kramer JM, Anstrom KJ. Using inverse probability-weighted estimators in comparative effectiveness analyses with observational databases. *Med Care*. 2007;45(10)(suppl 2):S103-S107.
- Mantel N, Byer DP. Evaluation of response-time data involving transient states: an illustration using heart-transplant data. *JASA*. 1974;69(345):81-86.
- Ezekowitz JA, McAlister FA. Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials. *Eur Heart J*. 2009;30(4):469-477.
- Sox HC, Greenfield S. Comparative effectiveness research: a report from the Institute of Medicine. *Ann Intern Med*. 2009;151(3):203-205.
- Cherubini A, Oristrelli J, Pla X, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med*. 2011;171(6):550-556.
- Pitt B, Remme W, Zannad F, et al; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348(14):1309-1321.
- Fonarow GC, Albert NM, Curtis AB, et al. Associations between outpatient heart failure process-of-care measures and mortality. *Circulation*. 2011;123(15):1601-1610.
- Fonarow GC, Albert NM, Curtis AB, et al. Incremental reduction in risk of death associated with use of guideline-recommended therapies in patients with heart failure: a nested case-control analysis of IM-PROVE HF. *J Am Heart Assoc*. 2012;1(1):16-26.
- Hamaguchi S, Kinugawa S, Tsuchihashi-Makaya M, et al. Spironolactone use at discharge was associated with improved survival in hospitalized patients with systolic heart failure. *Am Heart J*. 2010;160(6):1156-1162.
- Hernandez AF, Hammill BG, Peterson ED, et al. Relationships between emerging measures of heart failure processes of care and clinical outcomes. *Am Heart J*. 2010;159(3):406-413.
- Vandenbroucke JP, von Elm E, Altman DG, et al; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology*. 2007;18(6):805-835.
- Dreyer NA, Schneeweiss S, McNeil BJ, et al; GRACE Initiative. GRACE principles: recognizing high-quality observational studies of comparative effectiveness. *Am J Manag Care*. 2010;16(6):467-471.
- Levine M, Ioannidis J, Haines T, Guyatt G, Harm (observational studies). In: Guyatt G, Rennie D, Meade MO, Cook DJ, eds. *Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice*. 2nd ed. New York, NY: McGraw-Hill; 2008:363-382. <http://www.jamaevidence.com/content/3346070>. Accessed September 30, 2012.