

Original Research

Evaluation of aldosterone antagonist utilization in heart failure with reduced and preserved ejection fraction at an academic medical center

Daniel BRADLEY , Jean NAPPI 

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Abstract

Background: Aldosterone antagonists (AA) have historically been underutilized despite evidence that they reduce morbidity, mortality, and readmission rates to the hospital when used appropriately.

Objective: We sought to determine if AAs were being prescribed in accordance with the 2013 ACCF/AHA guidelines and if there was any benefit surrounding 30-day readmissions or 30-day mortality for patients taking AAs with heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF).

Methods: We performed a retrospective chart review of adult patients who were discharged between October 1, 2015 and February 1, 2016 with any ICD-10 code for heart failure to assess compliance with guideline directed medical therapy. At baseline, patients were stratified by HFpEF and HFrEF. Patients were excluded if they died during the admission, discharged with hospice care, received a heart transplant or ventricular assist device, if they were miscoded or left against medical advice. Descriptive statistics, and Chi Square were used to evaluate the data.

Results: We reviewed 601 patient charts for eligibility in our study, and determined 438 met the criteria for inclusion. Ninety-seven patients (22%) received an AA. Within the HFrEF group, only 37% of patients who were eligible per 2013 ACCF/AHA guidelines, received an AA at time of discharge. Fourteen percent of HFpEF patients were discharged on an AA. We found a trend towards decreased rates of our 30-day outcomes in patients who took AAs in both the HFpEF and HFrEF groups.

Conclusions: AAs were underutilized during the timeframe we evaluated, despite the evidence for their use.

Keywords

Heart Failure; Mineralocorticoid Receptor Antagonists; Drug Utilization; Guideline Adherence; Clinical Audit; United States

INTRODUCTION

Cardiac remodeling and the progression of heart failure driven by the renin-angiotensin-aldosterone system (RAAS) has been an area of interest for over five decades.¹ Each year our knowledge base becomes more nuanced, and the complex roles of each hormone become further elucidated. Even though there is now evidence of local production of aldosterone by failing cardiac tissues, aldosterone production is primarily dependent upon the activation of systemic RAAS.^{1,2}

In heart failure, this cascade of actions is more detrimental than supportive as hypoperfusion is primarily related to a decreased cardiac output, secondary to decreased pump function; not hypotension. With the increase in circulating volume, which may promote systemic congestion, aldosterone directly promotes myocyte hypertrophy, fibrosis, atherosclerosis, reduced baroreceptor sensitivity, and decreased nitric oxide availability among other deleterious effects.^{1,3-5} Without intervention, a failing heart will become victim of the body's own compensatory mechanisms in an uncontrolled downward spiral of further hormonal activation, fluid retention, tissue remodeling and pump failure.

Today, we have a large base of clinical evidence to support the use of aldosterone antagonists (AAs) in patients with

varying degrees of heart failure with reduced ejection fraction (HFrEF). Over the last 20 years multiple landmark trials have reported encouraging findings which have since been used to synthesize the current guidelines for HFrEF treatment. We suspected that these medications may remain as underutilized as they were years ago.⁶ Underutilization of AAs suggest a significant misstep in treatment considering the impact this class of drugs has on morbidity, mortality and readmission rates. In 1999 the "Randomized Aldactone Evaluation Study" (RALES) showed that in patients with an ejection fraction of <35% and New York Heart Association (NYHA) III-IV symptoms, spironolactone led to a 30% reduction in all-cause mortality.⁷ Four years later the "Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction" (EPHESUS) trial demonstrated a 15% mortality reduction with eplerenone.⁸ "Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms" (EMPHASIS-HF) demonstrated a reduction in the composite outcome of cardiovascular deaths and HF related hospitalizations in patients with NYHA class II symptoms.⁹ Given the broad range of patient characteristics, among these three trials, the current guidelines recommend utilization of AAs in most patients with HFrEF, unless a contraindication is present.

The 2017 ACC/AHA/HFSA focused update addressed the use of AAs in patients with heart failure with preserved ejection fraction (HFpEF). Patients with HFpEF may have different risk factors, and varying etiology of disease, but have from similar symptoms to those with HFrEF.¹⁰ Prior to the TOPCAT trial, the effects of AAs had not been

Daniel BRADLEY. PharmD. Clinical Pharmacist. Medical University of South Carolina. Charleston, SC (United States).

Jean NAPPI. PharmD, FCCP, BCPS (AQ-Card). Professor. Medical University of South Carolina. Charleston, SC (United States).



extensively studied in a randomized controlled composite outcome trial in patients with HFpEF.¹¹ The composite primary outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure in patients receiving spironolactone was not significantly different from those receiving placebo.¹¹ Despite the composite outcome results, a significant benefit was seen with spironolactone in reduction of heart failure related hospitalizations. Amid controversy regarding the severity of baseline illness in patients between the two regions within the study, a post hoc/subgroup analysis was performed. After further investigation a positive finding for the composite outcome was found for patients in the American region.¹² Thus far, no other study has since provided evidence to show that AAs may reduce mortality in patients with HFpEF.¹³ Today, it is suggested that nearly 50% of patients who have a diagnosis of heart failure, retain a preserved ejection fraction. Despite the lack of a statistically significant benefit, the TOPCAT trial at least suggests that AAs may be an appropriate intervention. The phase 4 SPIRRIT study looking at the use of spironolactone in HFpEF should help clarify this issue.¹⁴

We sought to characterize the use of AAs at our institution in patients with a heart failure diagnosis. We hypothesized that the use of AAs would be less frequent than the

guidelines would recommend. We collected data on 30 days outcomes in both HFrEF and HFpEF patients to see if prescribing AAs would be of benefit.

METHODS

We designed a retrospective chart review to determine if our utilization of AAs corresponded with the number of patients that would be considered eligible for therapy per guideline recommendations. As AA use is considered level IA and IB evidence in the 2013 ACCF/AHA guidelines for HFrEF, we wanted to ensure the patients who could benefit from these medications were receiving them.¹⁵ Due to the findings in the subgroup analysis of the TOPCAT trial, we further divided our patients in two groups; those with HFrEF and those with HFpEF. Ultimately, this decision was made to illuminate a possible link between AA use at discharge, and readmission rate or mortality within HFpEF or HFrEF groups at our institution.

Eligible patients included adults 18 years or older who were discharged from the hospital between October 1, 2015 and February 1, 2016 with an ICD-10 code that indicated any diagnosis of heart failure. This included both new and repeated admissions for heart failure. These dates were

Characteristic	HFrEF (n = 154)	HFpEF (n = 284)	p-value
Age. years (mean)	63	69	<0.0001
Female gender. n (%)	49 (31.8)	148 (52.1)	<0.0001
Height. cm (mean)	172.1	167.5	0.002
Weight. kg (mean)	85.8	86.4	0.824
Race. n (%)			0.184
White	78 (50.6)	165 (58.1)	
Black	71 (46.1)	115 (40.5)	
Other	5 (3.2)	4 (1.4)	
Heart rate. beats/min	79	77	0.229
Blood pressure. mmHg			
Systolic	118	130	<0.0001
Diastolic	70	72	0.308
Left ventricular ejection fraction. %	28	59	<0.0001
Serum K ⁺ mmol/L	4.2	4.1	0.103
Serum creatinine. mg/dL	1.8	1.7	0.563
Estimated glomerular filtration rate	47	46	0.888
Medications. n (%)			
Loop diuretic	103 (66.9)	168 (59.2)	0.112
ACE inhibitor	85 (55.2)	91 (32)	<0.0001
ARB	22 (14.3)	44 (15.5)	0.736
ARB/neprilysin inhibitor	1 (0.6)	1 (0.4)	0.66
Aspirin	93 (60.4)	175 (61.6)	0.801
P2Y12 inhibitor	20 (13)	47 (16.5)	0.323
Anticoagulant	61 (39.6)	85 (29.9)	0.04
Hydralazine	24 (15.6)	34 (12)	0.287
Nitrate	31 (20.1)	45 (15.8)	0.258
Potassium supplement	34 (22.1)	68 (23.9)	0.659
Digoxin	27 (17.5)	21 (7.4)	0.001
Statin	102 (66.2)	180 (63.4)	0.552
Beta-blocker	132 (85.7)	209 (73.6)	0.004
IV inotrope	10 (6.5)	2 (0.7)	<0.0001
Medical History. n (%)			
Diabetes mellitus	78 (50.6)	131 (46.1)	0.366
Hypertension	124 (80.5)	257 (90.5)	0.002
Ischemic heart disease (Unstable angina/myocardial infarction/coronary artery disease/ history of coronary artery bypass graft)	82 (53.2)	152 (53.5)	0.956
Device (Implantable cardioverter defibrillator/Pacemaker)	57 (37)	60 (21.1)	<0.001
Chronic kidney disease	56 (36.4)	106 (37.3)	0.842
Atrial fibrillation	59 (38.3)	106 (37.3)	0.839

	HFrEF (n = 154)	HFpEF (n = 284)	p-value
Prescribed Aldosterone Antagonist (AA) at hospital discharge	57 (37%)	40 (14.1%)	<0.001
Started on AA after hospital discharge in clinic	3 (2%)	1 (0.3%)	
Of patients NOT on Aldosterone Antagonists	HFrEF, not on AA (n=97)	HFpEF, not on AA (n=244)	-
Indicated (HFrEF) and not on AA	54 (56%)	-	-
HFrEF not on AA due to contraindication	43 (44%)	-	-
Not on AA with HFpEF diagnosis	-	175 (72%)	-
Not on AA with HFpEF and other contraindication	-	69 (28%)	-

selected to provide a pool of roughly 600 patients from the time the EPIC electronic medical record was adopted at our institution. Patients were excluded if they were pregnant, had a planned admission (eg, O.R.), died during the admission or were discharged with hospice care, had received a heart transplant or ventricular assist device, if they had no clear evidence of heart failure (miscoded) or if they left against medical advice. We considered those with the most recent measured ejection fraction prior to or during admission of $\leq 40\%$ as patients with HFrEF. Despite the classification of borderline HFpEF (EF 41-49%), we decided to consider patients with an EF above 40% to have HFpEF. We used the current ACCF/AHA guidelines to determine the appropriateness of AA therapy. If patients had acute kidney injury, hypotension, eGFR < 30 mL/minute/1.73 m² or creatinine > 2.5 mg/dL (men) or > 2 mg/dL (women), potassium > 5 mEq/L or history of hyperkalemia they were deemed ineligible for AAs. Additionally, we determined if a patient was started on an AA in clinic within 14 days from discharge. Occasionally, patients are not quite stable enough at discharge to start new medications, and initiation or re-initiation of an AA may be indicated, but deferred to the primary care physician or HF clinic provider as the patient continues to improve while other goal directed medications are titrated. As noted in the 2017 Pathways for Optimization of Heart Failure Treatment, it is not necessary to achieve target doses or maximally tolerated doses of other drugs before adding an AA.¹⁶ For patients that met our criteria, investigators manually pulled all variables from patient charts via EPIC universe. This information was then pooled into a secure datasheet available only on a secure network. Baseline characteristics were compared between HFpEF and HFrEF using chi-square tests when assessing differences between the groups with categorical variables, and t-tests for data comprised of continuous variables. These analyses were performed using the statistical functions of Microsoft excel and SPSS statistical software. This study was approved by the institutional review board.

RESULTS

A total of 601 patients with a diagnosis of heart failure from the pre-specified time period were preliminarily included. After evaluation and assessment by the research team, 438

patients were determined to meet criteria for the final data extraction to be further analyzed. Baseline demographic data are presented in Table 1. There were several significant differences noted between the HFrEF and HFpEF patients. In addition to differences in ejection fraction, HFpEF patients were older, more often female, had higher systolic blood pressure, and received an ACE inhibitor, beta blocker, digoxin and IV inotrope less frequently.

Table 2 shows the utilization of AAs in our patient population. The utilization of AAs was significantly more frequent in patients who had HFrEF (37%) compared with that of patients with HFpEF (14.1%). Of the patients who had HFrEF and were not already on an AA over half were considered eligible at the time of observation per the 2013 ACCF/AHA guideline recommendations. Additionally, if we consider the same criteria and apply it to patients with HFpEF not receiving an AA, a majority of patients (72%) would be considered 'eligible' for therapy if there were a similar guideline recommendation as that seen with HFrEF. The remaining patients (28%) with HFpEF had a contraindication to an AA.

Table 3 presents the rates of readmission and death at 30 days. Rates of readmission within 30 days of discharge were assessed within each group and between those who received AAs and those who did not. Among all patients readmitted within 30 days, 15 patients had HFrEF, and 17 patients had HFpEF (9.7% and 6%, p=0.149). Within the HFrEF group, 7% of patients who were readmitted were taking an AA, versus 11.3% for those not taking an AA. Within the HFpEF group, no patients were readmitted within 30 days that were taking AAs, while 7% of patients not taking AAs were readmitted. These differences were not statistically significant.

Additionally, rate of death within 30 days of discharge was assessed within each group and between those who received AAs and those who did not. Among all patients, death within 30 days was observed in 8 patients with HFrEF and in 6 patients with HFpEF (5.2% and 2.1%, p=0.08). Within the HFrEF group, 1.8 % of patients died within 30 days who were taking an AA versus 7.2% of patients who were not taking an AA. Within the HFpEF group, no patients who were taking an AA died within 30 days of discharge, while 2.5% of patients who were not taking an AA died. Again, the differences were not statistically significant.

Readmission/Death between AA and NO AA		Prescribed AA	Not on AA	p-value
Readmissions	HFrEF readmitted within 30 days	4 (7%)	11 (11.3%)	0.382
	HFpEF readmitted within 30 days	0 (0%)	17 (7%)	0.085
Deaths	HFrEF death within 30 days	1 (1.8%)	7 (7.2%)	0.14
	HFpEF death within 30 days	0 (0%)	6 (2.5%)	0.316

Only two patients were receiving eplerenone, while the vast majority (98%) were prescribed spironolactone. The mean dose of spironolactone per day was 27.5 mg (SD 18.7). Finally, only four patients in total were started on an AA in a clinic appointment within 14 days of discharge (three with HFrEF, and one with HFpEF).

DISCUSSION

We evaluated a diverse group of patients with varying degrees of heart failure prior to discharge in the hopes that we would be able to establish how well we may be using a potentially underutilized medication with clear disease modifying benefits. A few interesting observations were noted within our study population. First, the presence of nearly twice as many patients with HFpEF compared with HFrEF is not reflective of the literature.¹⁷ This likely is a direct result of our exclusion criteria eliminating many sick patients and our choice to use an ejection fraction of 40% as the cutoff for HFpEF vs. HFrEF, with no grouping for intermediate heart failure. Secondly, there was a statistically significant increase in the utilization of anticoagulants in patients with HFrEF, but the rates of atrial fibrillation between groups were roughly equal. This discrepancy would suggest that our population of HFrEF patients had a higher rate of venous thrombosis or pulmonary embolism, though these variables were not explicitly recorded in our study. These results correspond with a subset of existing literature that proposes risk of VTE is directly related to left ventricular function.¹⁸

In similar fashion to the traditional epidemiology of HFpEF, our patients with HFpEF were predominantly older, female, and had higher rates of hypertension when compared with the HFrEF group.^{15,19} The utilization of ACE inhibitors, beta-blockers, hydralazine and nitrates was seen with higher frequency in the HFrEF group, though only ACE inhibitors and beta-blockers were significantly different. This mirrors expectations as these medications comprise the core of our current goal directed medical therapies for HFrEF. Though significantly more patients were on chronic IV inotropes in the HFrEF group, it is worth noting that two patients in the HFpEF group were on chronic IV inotropes. It is possible that these two patients previously had acutely decompensated HFrEF and now have ejection fractions that have recovered secondary to inotrope usage or for other reasons. This points out a limitation of our observational study, but suitably describes heart failure as a syndrome with a continuum of symptoms and objective measurements of disease severity that are rarely static.²⁰ Finally, use of digoxin and cardiac devices was observed with significantly higher incidence in patients with HFrEF compared with HFpEF.

Over half of the patients who met guideline directed criteria for the utilization of an AA at time of observation were not receiving one. Interestingly, the CHAMP-HF registry observed an AA utilization rate of 33%, which is in line without results.²¹ In most instances aldosterone antagonists were avoided due to "soft" blood pressures, laboratory abnormalities, kidney dysfunction or due to titration of other goal directed medications. However, with appropriate prescribing and monitoring, the benefits of treatment often outweigh the risks. The current utilization

of AAs at our organization would suggest there is significant room for improvement in the rate of compliance per ACCF/AHA guidelines for HFrEF. This pattern carries significant weight considering the known morbidity, mortality and readmission benefits as seen with patients in the RALES, EPHESUS, and EMPHASIS-HF trials.

The TOPCAT trial suggests this class of medications can at least prevent heart failure related admissions, and possibly improves morbidity and mortality in patients diagnosed with HFpEF using natriuretic peptide levels. While our results did not reach a statistically significant difference, this is likely due to inadequate power. The data from our institution may support the known readmission or mortality benefits as seen in larger trials, as there was a trend in a similar direction among patients with both HFrEF and HFpEF.

Understanding that the prescribing of AAs may not be as frequent as the guidelines recommend, methods to improve compliance with guidelines will undoubtedly help our patients. Considering that the majority of the patients we evaluated were discharged from inpatient cardiology services, we would expect that patients who meet guideline criteria have been assessed for initiation of AAs. As these services are run by a constantly rotating cadre of medical residents and interns, regular education on guideline directed medical therapy from the rounding pharmacist staff is likely the most direct and reliable form of correction. Pharmacists at our institution currently round with the cardiology teams and a majority of other inpatient services on a daily basis and have regular opportunities to impact patient care. Pharmacists share responsibility with senior physicians in directly educating our younger medical colleagues, specifically with regard to pharmacology, and therapeutics of these goal directed medications. Simultaneously, the implementation and creation of an algorithm congruent with heart failure guideline directed medical therapy would provide an easily accessible physical reference for each prescriber that spends a month with the cardiology team. These may be two of the most direct and easily implemented solutions, but new ideas are clearly needed.

Limitations

Certainly, many limitations exist when looking at these outcomes in this study and we are cautious in comparing an observational study to randomized prospective trials. In addition to potentially not meeting power (no power calculation was performed due to the intent of the study), the period of 30 days was likely too short to appreciate a true statistical difference in rates of all cause death or readmissions. For example, the three HFrEF landmark trials specifically evaluated morbidity and mortality over many months, but only within the EPHESUS trial was a mortality benefit appreciated 30 days after randomization.²² Additionally, it is nearly impossible to account for all deaths or readmissions of a cohort without prospective follow up considering the possibility of readmission or death at another hospital. Finally, we were unable to adjust our data for confounding variables (e.g. other goal directed medications) due to the relatively low number of events.

CONCLUSIONS

We demonstrated that there is significant underutilization of AAs in patients admitted with acute decompensated heart failure in our institution which is similar to national data. Consistent education efforts are still necessary to ensure our patients are receiving guideline directed medical therapy with AAs, which confer significant improvement in various patient-oriented outcomes. Increased prescribing may improve heart failure outcomes across the country, not only for patients with HFrEF, but also for patients with HFpEF.

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CONFLICT OF INTEREST

No real or apparent conflicts of interest to disclose, and there was no funding provided.

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