Patterns of Use and Clinical Outcomes with Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Acute Heart Failure and Changes in Kidney Function: An Analysis of the Veterans' Health Administrative Database

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Keywords

Angiotensin-converting enzyme inhibitors · Angiotensin receptor blockers · Acute heart failure · Readmissions · Mortality · Outcomes

Abstract

Objective: The aim of the study was to determine patterns and predictors of utilization of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs) in patients with acute heart failure (AHF) and changes in kidney function at admission, hospitalization, and discharge in relation to clinical outcomes. **Methods:** This retrospective analysis of the Veterans' Health Administration data (2016) included patients with heart failure (HF) with reduced ejection fraction who were hospitalized. Patients with an estimated glomerular filtration <15 cm³/min/1.73 m² and those on dialysis were excluded. Patients were categorized based

on the use of ACEI/ARB as continued, initiated, discontinued, or no therapy. Multivariable logistic regression evaluated predictors of being discharged home on an ACEI/ARB. Cox regression analysis evaluated outcomes (30 and 180-day mortality/HF readmissions). **Results:** 3,652 patients were included, of which 37% of patients hospitalized for AHF had ACEI/ARB discontinued on admission, or not initiated. After adjusting for age, blood pressure, and serum potassium, a per-unit increase in admission serum creatinine (SCr) was independently associated with lower rates of continuation or initiation of ACEI/ARB odds ratio 0.51 95% confidence interval (CI) (0.46–0.57). Discharge on ACEI/ARB was independently associated with lower odds of 30- and 180-day mortality hazard ratio (HR) 0.36 95% CI (0.25–0.52), and HR 0.23 95% CI (0.19–0.27), respectively. **Conclusion:** Higher SCr at admission is an important determinant of ACEI/ARB being

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discontinued or withheld in patients admitted with AHF. ACEI/ARB at discharge was associated with lower mortality in patients with AHF.

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Introduction

The inhibition of the renin-angiotensin-aldosterone system (RAAS) plays a key role in reducing morbidity and mortality in patients with heart failure (HF), particularly in those patients with HF with reduced ejection fraction (HFrEF). The benefits of the RAAS inhibition (RAASi) have been proven in landmark trials resulting in their incorporation as key elements of guideline directed medical therapies (GDMTs) for HFrEF [1–3]. However, there are limited high-quality data to guide use in terms of initiation, continuation, or withdrawal of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) in the setting of acute heart failure (AHF) in patients with HFrEF, especially in those with fluctuating kidney function while simultaneously undergoing decongestion in the inpatient setting [4]. While continuation of RAASi therapy after hospital discharge in patients with HFrEF has been associated with lower mortality and re-admission rates in prior observational studies [5], there is still a high rate of discontinuation of ACEI/ARB therapy during AHF due to concerns for worsening kidney function, hypotension, and hyperkalemia, especially in patients undergoing decongestion [4, 6, 7]. Therefore, we aimed to investigate further the patterns of ACEI/ARB use among hospitalized patients with AHF in those with HFrEF and effect on clinical outcomes of mortality and HF readmissions, in the context of active decongestion and changes in kidney function.

Methods

The Institutional Review Board at the Columbia VA Health Care System approved the project. Veterans' Health Administration (VHA) electronic health record data from January 1, 2016 to December 31, 2016 were accessed to obtain national VHA data using the Veterans' Integrated Networking and Computing Infrastructure. All patients with any diagnosis related to HFrEF were identified (see online suppl. appendix for details of diagnostic code methodology; see www.karger.com/doi/10.1159/000519014 for all online suppl. material). We only included patients with index admission for acute systolic and/or acute on chronic systolic HF defined as the first AHF hospitalization for a unique veteran in 2016, with a length of stay >48 h (to eliminate observation admissions or early deaths) and with available inpatient creatinine values measured on admission and on discharge to help categorize worsening renal function

(WRF) during the hospitalization. Patients included should have an estimated glomerular filtration rate >15 mL/min/1.73 m² and not on maintenance hemodialysis at the time of admission.

Patients were categorized by pattern of ACEI/ARB use during the inpatient stay. Patients were categorized as continued if they were on an outpatient ACEI/ARB at any time point in the 12 months prior to the index admission, and there was evidence of medication administration during the inpatient stay; initiated if there was no evidence of outpatient ACEI or ARB in the 12 months prior to the index admission but ACEI or ARB administered during the inpatient stay; discontinued outpatient therapy if there was a prescription of outpatient ACEI or ARB in the 12 months preceding the index admission but no administration of ACEI/ARB during the inpatient stay, and if an ACEI/ARB was discontinued on hospitalization, it can be reinitiated on discharge; finally, no therapy if there was neither outpatient nor inpatient in the record. ACEI dosing was normalized to lisinopril equivalent dosing, and ARB to losartan equivalent dosing. Contraindication to ACEI/ARB was defined as any of the following: systolic blood pressure ≤90 mm Hg, potassium ≥5 mEq/L, or serum creatinine (SCr) ≥2.5 mg/dL [8]. Other medications evaluated included β-blockers, loop diuretics, thiazide-type diuretics, and mineralocorticoid receptor antagonists. The time frame of inclusion (first hospitalization in 2016) was just after Food and Drug Administration approval for the first angiotensin receptor neprilysin inhibitors (ARNIs) in the USA. No patients had evidence of Veterans Affairs (VA) provided ARNI prior to nor during hospitalization. A total of 6 patients had evidence of ARNI prescription within 7 days following discharge, and this was included in the RAASi at discharge category. No analysis was done for ARNI on admission or hospitalization, but it was included in the discharge analysis.

WRF was determined and defined as worsening renal function on admission (WRF-A) which was >0.3 mg/dL rise in creatinine from baseline values within the past 12 months, while worsening renal function during hospitalization (WRF-H) was defined as >0.3 mg/dL rise in creatinine from admission. Significant reduction in weight was defined as >13 lb weight change during the course of the hospitalization, while a nonsignificant change in weight was defined as <13 lb weight change (lower limit of terciles of weight change in population); this is similar to the characterization of "significant weight loss" in the secondary analysis from the Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure Trial [9]. Patients in the current cohort were then divided into 4 mutually exclusive groups: no change in renal function + weight loss ≥13 pounds (lbs); no change in renal function + weight loss <13 lbs, or weight gain; WRF during admission + weight loss ≥13 lbs; and WRF during admission + weight loss <13 lbs, or weight gain.

Additional information collected from patient records included clinical and laboratory data (see online suppl. appendix; online suppl. Tables 1, 2); ejection fraction was not available in this data set. Data on b-type natriuretic peptide (BNP; in picograms per milliliter) and N-terminal pro-BNP (NT-pro-BNP; in picograms per milliliter) were extracted from all VA hospitals depending on local default test type. Outcomes included 30- and 180-day post-discharge all-cause mortality and readmission for HF only.

Statistical Analysis

All analyses were conducted using R v 3.6.1 (2019-07-05) (<https://cran.r-project.org/>) via the integrated development envi-

Table 1. Demographic and clinical profile of the sample population

	ACEIs/ARBs therapy group				p value
	continue ACEI/ARB	initiate ACEI/ARB	discontinue ACEI/ARB	no therapy	
N	1,715	594	717	626	
Demographics					
Age, years, mean (SD)	71.10 (10.15)	71.89 (11.50)	72.33 (10.92)	75.44 (11.37)	<0.001
Male, N (%)	1,693 (98.7)	581 (97.8)	704 (98.2)	615 (98.2)	0.444
Race, N (%)					
White	1,153 (67.2)	412 (69.4)	497 (69.3)	429 (68.5)	0.14
Black or African American	93 (5.4)	35 (5.9)	34 (4.7)	49 (7.8)	
Other	469 (27.3)	147 (24.7)	186 (25.9)	148 (23.6)	
Ethnicity, N (%)					
Hispanic or Latino	106 (6.2)	34 (5.7)	42 (5.9)	34 (5.4)	0.534
Not Hispanic or Latino	1,559 (90.9)	545 (91.8)	651 (90.8)	564 (90.1)	
Unknown	50 (2.9)	15 (2.5)	24 (3.3)	28 (4.5)	
Baseline Co-morbidities, N (%)					
Diabetes mellitus	569 (33.2)	93 (15.7)	242 (33.8)	146 (23.3)	<0.001
Hypertension	1,077 (62.8)	313 (52.7)	366 (51.0)	265 (42.3)	<0.001
Coronary artery disease	1,156 (67.4)	315 (53.0)	497 (69.3)	381 (60.9)	<0.001
Peripheral arterial disease	53 (3.1)	20 (3.4)	33 (4.6)	19 (3.0)	0.274
Cerebrovascular accident	187 (10.9)	52 (8.8)	75 (10.5)	61 (9.7)	0.485
Chronic obstructive pulmonary disease	680 (39.7)	206 (34.7)	265 (37.0)	241 (38.5)	0.163
CKD stage					
Stage 1	184 (10.7)	132 (22.2)	36 (5.0)	55 (8.8)	<0.001
Stage 2	714 (41.6)	278 (46.8)	164 (22.9)	166 (26.5)	
Stage 3a	445 (25.9)	96 (16.2)	184 (25.7)	124 (19.8)	
Stage 3b	284 (16.6)	65 (10.9)	204 (28.5)	163 (26.0)	
Stage 4	88 (5.1)	23 (3.9)	129 (18.0)	118 (18.8)	
Prior heart failure diagnosis	1,476 (86.1)	294 (49.5)	654 (91.2)	479 (76.5)	<0.001
History of smoking	475 (27.7)	180 (30.3)	173 (24.1)	177 (28.3)	0.084
Current smoking	175 (10.2)	80 (13.5)	49 (6.8)	58 (9.3)	0.001
Admission diagnosis					0.004
Acute systolic heart failure	298 (17.4)	194 (32.7)	115 (16)	123 (19.6)	
Acute on chronic systolic heart failure	1,417 (82.6)	400 (67.3)	602 (84)	503 (80.4)	
Baseline laboratory data, mean (SD)					
Potassium, mEq/L	4.16 (0.47)	4.18 (0.47)	4.20 (0.47)	4.15 (0.47)	0.202
Creatinine, mg/dL	1.33 (0.46)	1.23 (0.45)	1.65 (0.60)	1.65 (0.67)	<0.001
SBP, mm Hg	126.98 (18.16)	130.42 (18.10)	122.38 (17.70)	125.31 (18.19)	<0.001
Diastolic blood pressure, mm Hg	74.38 (11.04)	76.09 (10.97)	71.33 (10.13)	71.85 (11.54)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; SD, standard deviation; SBP, systolic blood pressure; CKD, chronic kidney disease.

ronment R-Studio© (version 1.3.1093; RStudio, PBC). The packages utilized included *base*, *odbc*, *stats*, *survival*, *survminer*, *ggplot2*, *Publish*, and *TableOne*. Descriptive statistics were performed to compare baseline demographic and clinical characteristics. Continuous variables that were normally distributed were evaluated utilizing parametric techniques, and those that were non-normally distributed were analyzed by nonparametric techniques. Categorical variables were evaluated utilizing χ^2 statistics (if expected cell size <5, Fisher's exact test). The primary analysis was performed with the 4 groups divided by inpatient ACEI/ARB status. Group-wise analysis of variance was performed, and analysis of baseline and inpatient characteristics was done. Potentially significant pre-

dictors of outcomes, with $p < 0.1$, were utilized to identify potential variables to be included in the multivariable analysis. After identification of predictor variables that met the aforementioned univariable criteria, multivariable Cox regression analysis was performed for the outcomes of mortality/HF readmission at 30 and 180 days, in patients who survived the index hospital admission. Visual assessment of the Kaplan-Meier curves was done to help determine proportional hazards assumption. Logistic regression was utilized to evaluate predictors of being discharged home on an ACEI/ARB. For renal function, WRF-A was added to the multivariate analyses compared to stable renal function on admission; WRF-H was considered with decongestion as per the 4 categories mentioned earlier.

A sensitivity analysis examining decongestion as a function of a natriuretic peptide cutoff (based on a Heart Failure Association of the European Society of Cardiology position paper on the use of diuretics in heart failure with congestion) [10] was performed. For this analysis, a follow-up BNP <300 ng/mL or NT-pro-BNP <1,500 ng/mL was considered evidence of $\leq$ "mild" congestion. This categorization required the presence of at least 2 natriuretic peptide readings ($N = 953$ [28% of the entire population]). Only 180-day mortality was examined in a Cox proportional hazards model. A 2-sided p value <0.05 was considered statistically significant, except for univariate predictor selection ($p < 0.1$).

Results

Baseline

A total of 26,091 patients were screened, after exclusions applied (see online suppl. Fig. 1) we arrived at the final sample of 3,652 patients with a hospitalization for AHF in 2016 in the VHA. Of the 3,652, there were 1,715 (47%) patients who continued ACEI/ARB, 594 (16%) patients with new initiation of ACEI/ARB, 717 (20%) patients who discontinued ACEI/ARB, and 626 (17%) patients with no therapy (Table 1). Results are presented as differences across levels of the categorical variables. Patients in the no therapy group were older than those in the other groups ($p < 0.001$). There was a higher prevalence of a history of coronary artery disease, diabetes mellitus, and hypertension among those with pre-hospitalization ACEI/ARB use (continue and discontinue ACEI/ARB groups) ($p < 0.05$ for trends). Patterns of medication use prior to, during hospitalization, and immediately after discharge are displayed in online supplementary Table 1. At admission, 608 (17%) of the whole cohort had at least 1 possible criterion for contraindication to ACEI/ARB. Among discontinue ACEI/ARB or no therapy patients, 957 (26.2%) had no guideline-based contraindication (online suppl. Table 1).

Hospital Characteristics

The discontinue ACEI/ARB group had the lowest prevalence of loop diuretics (88.3%) and mineralocorticoid receptor antagonists (4.7%) ($p < 0.001$ for trend) (online suppl. Table 1). At admission (Fig. 1a; online suppl. Table 2),

Fig. 1. a Boxplot representation of SCr among ACEI/ARB utilization groups. **b** Boxplot representation of serum potassium among ACEI/ARB utilization groups. **c** Boxplot representation of blood pressure among ACEI/ARB utilization groups. ACEI, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; SCr, serum creatinine.

Table 2. Multivariable regression on predictors of ACEI/ARB use on discharge

Predictor of discharge on ACEI/ARB	OR	2.50%	97.50%
Continue ACEI/ARB	Ref		
Discontinue ACEI/ARB	0.19	0.16	0.24
Initiate ACEI/ARB	0.81	0.40	1.64
No therapy	0.09	0.04	0.18
On ACEI or ARB prior to admission	2.68	2.3	3.12
Stable renal function at admission	Ref		
WRF-A	1.07	0.78	1.47
WRF-H and weight change categories			
Reduction in weight + no WRF-H	Ref		
No reduction/gain in weight + no WRF-H	0.8	0.67	1.07
No reduction/gain in weight + WRF-H	0.52	0.38	0.72
Reduction in weight + WRF-H	0.84	0.69	1.03
Baseline CKD			
No (stage 1 or 2)	Ref		
Yes (stage 3a, 3b, or 4)	0.61	0.51	0.73

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; WRF-A, worsening renal function on admission; WRF-H, worsening renal function during hospitalization; CKD, chronic kidney disease; OR, odds ratio.

mean SCr (milligrams per deciliter) was higher in the discontinue ACEI/ARB (1.93) and no therapy (1.83) groups than that in continue ACEI/ARB (1.38) or initiation of ACEI/ARB (1.27) groups ($p < 0.001$ for trend). Correspondingly, more patients among the discontinue ACEI/ARB (14.8%) and no therapy groups (8.9%) met criteria for WRF-A ($p < 0.001$ for trend). WRF-H was observed in 48.7 and 45.4% in discontinue ACEI/ARB and no therapy, respectively, versus 36.4% in those continuing ACEI/ARB and 32% in those with new initiation ($p < 0.001$ for trend). There were no significant differences in blood pressure values at admission, or during admission among groups. Maximum observed potassium value was statistically higher in the discontinue ACEI/ARB and no therapy groups (online suppl. Table 2) (Fig. 1b, c). After adjusting for age, blood pressure, and serum potassium, a per-unit increase in admission SCr was independently associated with lower rates of continuation or initiation of ACEI/ARB OR 0.51 95% CI (0.46–0.57) (online suppl. Table 1). There was also no significant difference in change in weight or natriuretic peptide values during the admission across groups.

Discharge

The length of stay was significantly longer for patients in initiate ACEI/ARB (8.5 days) or in no therapy (8.1 days) groups than continue ACEI/ARB (5.6 days) and discontinue ACEI/ARB (7.8 days), $p = 0.001$ for trend across groups. At discharge, SCr was significantly differ-

ent among groups (Fig. 1a; online suppl. Table 2), with the highest value in the no therapy group (1.61 mg/dL) and the lowest in the initiate ACEI/ARB group (1.23 mg/dL). At discharge, NT-pro-BNP was significantly higher in the no therapy group than the other groups; despite a higher BNP value in the no therapy group at discharge, the difference across groups did not meet statistical significance. Change in weight over the course of the admission was not statistically different across groups. At discharge, only 505 (13.8%) had at least 1 criterion for contraindication to ACEI/ARB; 2323 (63.6%) had evidence of a filled prescription for ACEI/ARB/ARNI within 7 days following discharge (online suppl. Table 1). Patients in the discontinue ACEI/ARB and no therapy groups had the lowest likelihood (utilizing the primary definition of discharge ACEI/ARB/ARNI – within 7 days of discharge) of discharge on ACEI/ARB/ARNI as compared to those in continue ACEI/ARB group (Table 2).

An alternative definition of discharge on ACEI/ARB/ARNI included all patients who were on inpatient ACEI/ARB on the day of discharge, which reflects clinical practice in that patients on a chronic medication on the day of discharge are likely to be sent home on the medication (online suppl. Table 1). When this was considered, the proportion of patients in the continue ACEI/ARB and initiate ACEI/ARB groups increased from 40.3 to 86.7%, and 59.4–87.2%, respectively.

Table 3. Univariable analyses of outcomes

	ACEIs/ARBs therapy group				p value
	continue ACEI/ARB	initiate ACEI/ARB	discontinue ACEI/ARB	no therapy	
N	1,715	594	717	626	
Length of stay, days, mean (SD)	7.09 (5.60)	8.54 (9.23)	8.09 (8.18)	7.79 (7.16)	<0.001
Mortality, N (%)					
Inpatient	14 (0.8)	9 (1.5)	30 (4.2)	29 (4.6)	<0.001
30-day	83 (4.8)	38 (6.4)	82 (11.4)	61 (9.7)	<0.001
180-day	293 (17.1)	102 (17.2)	221 (30.8)	170 (27.2)	<0.001
365-day	497 (29.0)	162 (27.3)	315 (43.9)	246 (39.3)	<0.001
Readmission for heart failure, N (%)					
30-day	160 (9.3)	35 (5.9)	114 (15.9)	46 (7.3)	<0.001
180-day	370 (21.6)	72 (12.1)	154 (21.5)	85 (13.6)	<0.001
365-day	494 (28.8)	112 (18.9)	188 (26.2)	106 (16.9)	<0.001
Physiologic parameters					
Creatinine, mg/dL					
180-day, mean (SD)	1.51 (0.68)	1.43 (0.69)	1.96 (0.99)	1.97 (1.05)	<0.001
365-day, mean (SD)	1.54 (0.73)	1.43 (0.73)	2.03 (1.16)	2.24 (3.75)	<0.001
Potassium, meq/L					
180-day, mean (SD)	4.19 (0.51)	4.26 (0.49)	4.19 (0.49)	4.18 (0.47)	0.127
365-day, mean (SD)	4.17 (0.44)	4.19 (0.48)	4.20 (0.47)	4.21 (0.49)	0.615

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; SD, standard deviation.

Table 4. Multivariable regression on predictors of inpatient mortality

Inpatient mortality	OR	2.50%	97.50%
Continue ACEI/ARB	Ref		
Discontinue ACEI/ARB	3.76	1.84	7.70
Initiate ACEI/ARB	1.95	0.78	4.91
No therapy	4.15	2.01	8.55
Stable renal function at admission	Ref		
WRF-A	3.58	1.92	6.66
Age at admission	1.04	1.01	1.06
Presence of diabetes mellitus	1.68	1.00	2.82
Change in weight during admission			
Reduction in weight + no WRF-H	Ref		
No reduction/gain in weight + no WRF-H	2.15	0.93	4.98
No reduction/gain in weight + WRF-H	13.52	6.72	27.23
Reduction in weight + WRF-H	3.55	1.76	7.14
Baseline CKD			
No CKD (stage 1 or 2)	Ref		
Yes (stage 3a, 3b, or 4)	1.19	0.71	2.02

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; WRF-A, worsening renal function on admission; WRF-H, worsening renal function during hospitalization; CKD, chronic kidney disease; OR, odds ratio.

Outcomes

Table 3 displays the univariable analysis of outcomes. Inpatient mortality was lowest in the continue ACEI/ARB (0.8%) and initiate ACEI/ARB (1.5%) groups as compared

to discontinue ACEI/ARB (4.2%) and no therapy (4.6%) groups ($p < 0.001$ for trend) (Table 3). As compared to continue ACEI/ARB, discontinue ACEI/ARB (OR 3.76, 95% CI [1.84–7.70]) or no therapy (OR 4.15 95% CI [2.01–

Table 5. Multivariable regression of factors associated with clinical outcomes of HF readmission

	30-day events			180-day events		
	HR	2.50%	97.50%	HR	2.50%	97.50%
ACEI/ARB therapy during admission						
Continue ACEI/ARB	Ref					
Discontinue ACEI/ARB	1.72	1.32	2.23	1.15	0.93	1.41
Initiate ACEI/ARB	0.85	0.58	1.25	0.64	0.49	0.83
No therapy	0.84	0.59	1.21	0.82	0.62	1.07
Age at index admission	0.98	0.97	0.99	0.98	0.97	0.99
Discharge on ACEI/ARB/ARNI	1.46	1.14	1.88	1.30	1.07	1.59
Renal function						
Baseline CKD						
No (stage 1 or 2)	Ref					
Yes (stage 3a, 3b, or 4)	0.83	0.68	1.05	1.16	0.99	1.39
Reduction in weight + no WRF-H	Ref					
No reduction/gain in weight + no WRF-H	1.24	0.92	1.67	1.01	0.81	1.25
No reduction/gain in weight + WRF-H	1.29	0.87	1.91	0.80	0.56	1.13
Reduction in weight + WRF-H	1.02	0.79	1.33	1.14	0.95	1.37

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; WRF-H, worsening renal function during hospitalization; CKD, chronic kidney disease; HF, heart failure; HR, hazard ratio.

Table 6. Multivariable regression of factors associated with clinical outcomes of mortality

Predictor of mortality outcomes	30-day events			180-day events		
	HR	2.50%	97.50%	HR	2.50%	97.50%
ACEI/ARB therapy during admission						
Continue ACEI/ARB	Ref					
Discontinue ACEI/ARB	1.93	1.41	2.65	1.02	0.84	1.24
Initiate ACEI/ARB	1.48	0.99	2.22	0.79	0.62	0.99
No therapy	1.40	0.99	1.96	0.65	0.53	0.81
Age at index admission	1.04	1.03	1.06	1.03	1.02	1.04
Discharge on ACEI/ARB/ARNI	0.36	0.25	0.52	0.23	0.19	0.27
Renal function						
Baseline CKD						
No (stage 1 or 2)	Ref					
Yes (stage 3a, 3b, or 4)	0.70	0.53	0.92	0.87	0.74	1.02
Reduction in weight + no WRF-H	Ref					
No reduction/gain in weight + no WRF-H	1.71	1.21	2.40	1.37	1.12	1.67
No reduction/gain in weight + WRF-H	3.20	2.20	4.65	2.07	1.62	2.63
Reduction in weight + WRF-H	1.40	1.02	1.92	1.16	0.97	1.39

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; WRF-H, worsening renal function during hospitalization; CKD, chronic kidney disease; HR, hazard ratio.

8.55]) demonstrated higher odds of inpatient mortality in multivariable logistic regression analysis (Table 4).

In patients who survived the index hospitalization, discontinue ACEI/ARB was associated with a higher haz-

ard ratio (HR, 1.72; 95% CI [1.32–2.23]), of 30-day HF readmission than continue ACEI/ARB, whereas initiate ACEI/ARB use during the hospitalization was associated with lower 180-day HF hospitalization (HR 0.64; (95% CI

Fig. 2. Summary diagram. ACEI, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; ARNIs, angiotensin receptor neprilysin inhibitors; HR, hazard ratio; CI, confidence interval.

[0.49–0.83]) than continue ACEI/ARB (Table 5). In regard to mortality, as compared to continue ACEI/ARB, initiate ACEI/ARB (HR 0.79; 95% CI [0.62–0.99]) and no therapy (HR 0.65; 95% CI [0.53–0.81]) groups had lower all-cause mortality at 180 days following hospitalization.

Examining the interplay between congestion and WRF-H (Tables 5, 6), reduction in weight, regardless of coexistent WRF-H, was not associated with repeat HF hospitalization at 30 or 180 days. Lower weight loss during admission (or less decongestion) was associated with increased 30-day and 180-day all-cause mortality, regardless of the co-occurrence of WRF-H. WRF-H, despite significant weight loss, was associated with hazard of 30-day mortality (HR 1.40; 95% CI [1.02–1.92]) with lower effect sizes than significant weight loss without WRF-H (Table 6).

In a sensitivity analysis, decongestion was defined by a final natriuretic peptide value cutoff (BNP <300 pg/mL; NT-pro-BNP <1,500 ng/mL). When this was considered with the presence or absence of WRF-H, there was again seen a significant increase in all-cause mortality at 30 and

180 days for those without adequate decongestion and with WRF-H (30-day HR 1.22, $p = 0.02$; 180-day HR 2.75, $p < 0.001$); however, adequate decongestion without WRF-H was only associated with 180-day mortality (HR 1.83, $p = 0.03$).

Discharge on ACEI/ARB/ARNI (any prescription within 7 days of discharge) was independently associated with significantly lower odds of 30- and 180-day mortality with HR 0.36 (95% CI [0.25–0.52]) and HR 0.23 (95% CI [0.19–0.27]), respectively (Fig. 2); discharge on ACEI/ARB/ARNI was associated with an increased hazard for readmission for HF in this time frame. Other predictors are displayed in Tables 5 and 6.

Discussion

Based on this analysis of patterns and predictors of ACEI/ARB use and clinical outcomes in patients with AHF from a nationwide VA cohort, several observations

can made. Twenty percent of patients hospitalized for AHF had ACEI/ARB discontinued on admission, and 17% of those not previously on ACEI/ARB were not started on ACEI/ARB during hospitalization. This is consistent with the discontinuation rate in previous studies such as the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry where the discontinuation rate was 28% [6], while in the Get with the Guidelines Heart Failure (GWTG-HF) registry, it was 11.5% [7]. WRF appears to be a strong correlate of utilization of ACEI/ARB during the acute HF hospitalization. Finally, inpatient utilization of ACEI/ARB was one of the strongest predictors of discharge on ACEI/ARB/ARNI, which has consistently, as well as in this analysis, been associated with improved outcomes in patients with HFrEF [4, 8].

In our study, even though only 26% of patients had a documented contraindication to ACEI/ARB on admission, nonuse of ACEI/ARB was high, and initiation of therapy was low. In a recent analysis of the Change the Management of Patients With Heart Failure (CHAMP-HF) of patients with HFrEF, it was found that hospitalization for ADHF in itself was associated with discontinuation and de-escalation of all classes of guideline-directed medical therapy GDMT including ACEI/ARB [11]. This is not surprising as there is still paucity of data on the relationship of ACEI/ARB and decongestion in the setting of AHF [4].

In our patient population, those in whom ACEI/ARB was either discontinued or no therapy was given had a higher range of baseline SCr values and higher rates of WRF-A, likely representing type 1 cardiorenal syndrome (CRS) physiology [12]. This augments findings from the GWTG-HF registry. Krantz et al. [7] identified that “no concomitant renal insufficiency” was associated with a nearly 3 times likelihood of being discharged on an ACEI/ARB; however, distinction between pre-existing and acute hospitalization-associated kidney injury was not available [7]. The current analysis has identified that both pre-existing chronic kidney disease and WRF associated with the acute episode are independently associated with alterations in ACEI/ARB use, during hospitalization, and at discharge. The observation of less ACEI/ARB utilization in the setting of any WRF in general may reflect an inability to distinguish true AKI from benign hemodynamic fluctuations in the setting of diuresis. In the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial, a doubling of SCr in 11% of subjects taking enalapril was primarily related to diuretic use and hypotension but returned to within 30% of baseline values in most subjects [13]. Several other recent analyses have con-

firmed the lack of negative predictive value of WRF on acute HF outcomes, when this occurred in the context of appropriate and aggressive decongestion [14–17].

Concurrent with this emerging body of data, we found that there was a significant association with 30- and 180-day mortality among patients with no weight reduction or with associated weight gain, regardless of WRF-H status. This is in contrast with patients who have adequate reduction in weight where the mortality association was only limited to 30-day mortality with smaller effect sizes. These results point out that WRF alone per se is not necessarily associated with poor outcomes, especially if satisfactory decongestion is achieved [14–18]. This supports the need for continuation of ACEI/ARB in the AHF setting even in the setting of WRF as the latter may be reflective of successful therapy and not true kidney injury [19]. To this end, newer biomarkers of tubular injury may help distinguish the development of AKI in patients versus benign fluctuations in glomerular filtration markers [20, 21] and may assist with the initiation and maintenance of ACEI/ARB in AHF with concomitant decongestion.

Hypotension and hyperkalemia are often invoked as reasons for stopping ACEI/ARB [5, 22]. In our study, although the maximum observed potassium value was statistically higher in the discontinue ACEI/ARB and no therapy groups, there were no significant differences blood pressure values between ACEI/ARB use groups in our study. This is partly consistent with the findings from the GWTG-HF registry wherein blood pressure values were overall lower among those with ACEI/ARB discontinued or no therapy, but potassium elevations >5 meq/L predicted higher rates of ACEI/ARB discontinuation in the GWTG-HF analysis; however, these patients also had significantly higher rates of renal dysfunction [5]. Furthermore, in a separate single center study of 626 patients admitted with AHF, the major reasons for discontinuation of ACEI/ARB were similar with very low rates of hyperkalemia (2%). This was despite excluding patients on dialysis and those who presented with any type of shock [23]. In our study, in the multivariable analysis after adjusting for blood pressure and potassium levels, a per-unit increase in admission SCr was independently associated with lower rates of continuation or initiation of ACEI/ARB, making renal function still the strongest predictor of ACEI/ARB utilization.

Mortality benefits were also seen on those discharged on ACEI/ARB with lower mortality risk at 30 days and 180 days, with HR 0.36, 95% CI (0.25, 0.52) and HR 0.23 95% CI (0.19, 0.27), respectively. These findings align

with the mortality benefit with maintenance of RAASi in AHF seen in the previous studies [5, 24]. Another single-center analysis showed higher inpatient death and 6-month readmissions in patients with AHF with elevated RA pressures on right heart catheterization, who had ACEI/ARB discontinued or never initiated [23]. The protective effects with ACEI/ARB may reflect favorable modulation of the maladaptive RAAS in acute HF including in those with WRF from type 1 cardiorenal syndrome. In this study, patients for whom ACEI/ARB was discontinued had higher rates of 30-day heart failure readmissions and 30-day mortality suggesting potential benefit of RAAS modulation in these patients (see online suppl. Fig. 2). A peculiar finding in our study was that being discharged on ACEI/ARB was associated with higher readmission rates. Since use and continuation of ACEI/ARB correlated with renal function in our study, it is likely that patients discharged on ACEI/ARB tended to have higher SCr levels. These in turn may possibly reflect inadequate decongestion, which may be related to the observed increase in HF readmissions. Moreover, readmissions outside the VA health-care systems might not be captured, and there is a possibility of surveillance bias as these patients continued or initiated on ACEI/ARB may have the tendency to be followed up more closely in the outpatient setting.

Strengths and Limitations

This study is limited by the retrospective nature of the analysis. This was a veteran population, largely male and Caucasian; thus, generalizability to the wider general public may be limited. As an analysis of a database registry, it may be subject to limitations in diagnostic coding. Outpatient compliance to HF GDMT might be difficult to ascertain due to the nature and design of the study. Other hemodynamic metrics, specifically ejection fraction (EF), were not available for the analysis; despite high specificity of systolic HF diagnosis for EF <40%, some patients may have had EF >40%, thus limiting the evidence for ACEI/ARB use [25, 26]. Data on HF readmissions may be limited by surveillance bias as patients newly initiated on ACEI/ARB may be followed up more closely as an outpatient. Additional residual confounders include outpatient initiation of medical therapy in the follow-up period and/or interval placement of devices such as cardiac resynchronization therapy and/or presence of CardioMEMS. As with all observational datasets, these findings may be limited by unknown residual confounders and indication bias. Nevertheless, the study provides a real-world context with robust findings on the

mortality benefits of ACEI/ARB in a large sample patient population together with description of patterns of use in the setting of AHF. Moreover, this study examines the significance of WRF especially in this patient population that can potentially be due to cardiorenal syndrome of which treatment with ACEI/ARB may be beneficial.

Conclusions

A significant proportion of patients admitted for AHF have ACEI/ARB discontinued or withheld, with WRF remaining as the most important influencing factor. ACEI/ARB at discharge was associated with lower mortality in patients with AHF. Quality improvement initiatives and pragmatic trials are needed to enhance ACEI/ARB utilization in patients with AHF, with specific focus on addressing concerns about WRF during AHF.

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Statement of Ethics

This research project was reviewed and approved by the Institutional Review Board with IRB net ID 1484392 at the Columbia VA Health Care System. No informed consent applicable as this is a retrospective database review.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors were involved with the study conceptualization and design. R.O.M. was involved with study data extraction and analysis. The first draft was done jointly by R.O.M., K.B.L., P.T. E.P., M.S., S.B., C.H., W.H.W.T., M.V., and J.R., and they were all involved with revisions with different versions of the manuscript. All authors reviewed and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in both the main text and the online supplementary material. Further inquiries can be directed to the corresponding author.

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