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A Propensity-Matched Study of the Comparative Effectiveness of Angiotensin Receptor Blockers versus Angiotensin-Converting Enzyme Inhibitors in Heart Failure Patients Age ≥ 65 Years

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Abstract

The comparative effectiveness of angiotensin-converting enzyme inhibitors (ACEIs) versus angiotensin receptor blockers (ARBs) in real-world older heart failure (HF) patients remains unclear. Of the 8049 hospitalized HF patients ≥ 65 years discharged alive from 106 Alabama hospitals, 4044 received discharge prescriptions of either ACEIs (n=3383) or ARBs (n=661). Propensity scores for ARB use, calculated for each of 4044 patients, were used to match 655 (99% of 661) patients receiving ARBs with 661 patients receiving ACEIs. The assembled cohort of 655 pairs of patients was well-balanced on 56 baseline characteristics. During over 8 years of follow-up, all-cause mortality occurred in 63% and 68% of matched patients receiving ARBs and ACEIs respectively (hazard ratio {HR} associated with ARB use, 0.86; 95% confidence interval {CI}, 0.75–0.99; p=0.031). Among the 956 matched patients with data on left ventricular ejection fraction (LVEF), the association between ARB (versus ACEI) use was significant only in 419 patients with LVEF $\geq 45\%$ (HR, 0.65; 95% CI, 0.51–0.84; p=0.001) but not in the 537 patients with LVEF <45% (HR, 1.00; 95% CI, 0.81–1.23; p=0.999; p for interaction= 0.012). HRs (95% CIs) for HF hospitalization associated with ARBs use were 0.99 (0.86–1.14; p=0.876) overall, 0.80 (0.63–1.03; p=0.080) among those with LVEF $\geq 45\%$ and 1.14 (0.91–1.43; p=0.246) among those with LVEF <45% (p for interaction, 0.060). In conclusion, in older HF patients with preserved LVEF, a discharge prescription of ARBs (versus ACEI) was associated with lower mortality and a trend toward lower HF hospitalization, findings which need replication in other HF populations.

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Keywords

Heart failure; Older; Mortality; ACEI; ARB

Most heart failure (HF) patients are older adults and HF is the leading cause of hospitalization for older Medicare beneficiaries. Inhibition of the renin-angiotensin system (RAS) by angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II type 1 receptor blockers (ARBs) form the foundation of the evidence-based therapy for patients with HF and reduced ejection fraction (HF-REF).¹ National HF guidelines vary in their recommendations regarding whether ACEIs or ARBs should be used as the drugs of first choice.¹⁻³ The efficacy of ACEI and ARB has been compared in randomized clinical trials (RCTs) of patients with HF-REF and patients with post-myocardial infarction left ventricular systolic dysfunction.^{4, 5} However, these RCTs often excluded older HF patients and those with preserved ejection fraction (HF-PEF). In the current study, we examined comparative effectiveness of ACEIs versus ARBs on outcomes in real-world older HF patients with REF and PEF.

Methods

The current study was based on the Alabama Heart Failure Project (AHFP) registry which has been previously described.⁶ Briefly, the AHFP was conducted by the AQA, the quality improvement organization of Alabama as a quality improvement project. Extensive data on baseline demographics, medical history including use of medications, hospital course, discharge disposition including medications, and physician specialty were collected via chart abstraction from 8555 patients discharged from 106 Alabama hospitals with primary discharge diagnosis of HF from 1998–2001.⁶ Of the 8555 patients, 8049 were discharged alive. After excluding patients receiving both ACEIs and ARBs (n=93) and those receiving neither of these drugs (n=3314), the study sample consisted of the 4642 patients, of whom 4044 (87%) were aged ≥ 65 years. Discharge prescriptions of ACEIs were given to 3383 (84%) patients and 661 (16%) patients received discharge prescriptions of ARBs. Lisinopril was the most common ACEI (30% or 1028/3383) and losartan was the most common ARB (57% or 378/661).

The study was designed using propensity score matching to assemble a balanced cohort in which patients receiving ACEIs and ARBs would be balanced on baseline characteristics.⁷⁻¹² The probability for the receipt of ARBs was estimated for each of the 4044 patients using a non-parsimonious multivariable logistic regression model in which the receipt of ARBs was the dependent variable and 56 baseline characteristics were used as covariates.¹³⁻¹⁶ We then used a greedy matching protocol enabling us to match 655 of the 661 patients receiving ARBs with 655 patients receiving ACEIs thus assembling a cohort of 655 pairs of patients who were well-balanced on all 56 measured baseline characteristics.¹⁷⁻²⁰

Baseline characteristics were compared using Pearson Chi square and Wilcoxon rank-sum tests for the pre-match data, and McNemar's test and paired sample t-test for post-match comparisons, as appropriate. Absolute standardized differences that directly quantify bias in the means (or proportions) of covariates across the two treatment groups were estimated and findings expressed as a percentage of the pooled standard deviations were presented as Love plots.⁹⁻¹² Kaplan-Meier plots and Cox regression analyses were used to determine the association of discharge prescription of ARBs versus ACEI use with all-cause mortality and hospitalization during over 8 years of follow-up. A formal sensitivity analysis was conducted to quantify the degree of a hidden bias that would be required to explain away a

significant association among matched patients.²¹ Additional sensitivity analyses were conducted using multivariable-adjusted (using all covariates used in the propensity model) and propensity-adjusted Cox regression models using pre-match data of 4044 patients. All statistical tests were two-tailed with a p-value <0.05 considered significant. SPSS for Windows version 18 (Chicago, IL) were used for data analysis.

Results

Overall, matched patients (n=1310) had a mean ($\pm$ SD) age of 78 ($\pm$ 7) years, 69% women, 19% African Americans. Imbalances in baseline characteristics before matching and balances achieved after matching between patients prescribed with ACEIs and ARBs at discharge are displayed in Table 1 and Figure 1. Before matching, patients prescribed with ARBs were more likely to be women and had higher prevalence of hypertension and coronary revascularization, lower prevalence of atrial fibrillation and renal insufficiency, and similar prevalence in coronary artery disease and diabetes mellitus. They were also less likely to receive digoxin, but had no differences in the receipt of other drugs such as diuretics and beta-blockers. However, these differences were balanced after matching. Post-match Love plot data suggest substantial covariate balance across the groups for all measured covariates (i.e., absolute standardized differences <10% for all covariates after matching; Figure 1).

All-cause mortality occurred in 63% and 68% of matched patients receiving ARBs and ACEIs respectively (hazard ratio {HR} when ARB use was compared with ACEI use, 0.86; 95% confidence interval {CI}, 0.75–0.99; p=0.031; Table 2 and Figure 2a). A hidden covariate that is a near-perfect predictor of mortality would need to decrease the odds of discharge prescription of ARBs by 7.7% to potentially explain away this association. Among the 956 matched patients with data on EF, the association between ARB use (versus ACEI use) was significant only in 419 patients with LVEF $\geq$ 45% (HR, 0.65; 95% CI, 0.51–0.84; p=0.001; Figure 2b) but not in the 537 patients with LVEF <45% (HR, 1.00; 95% CI, 0.81–1.23; p=0.999; Figure 2c). This difference was statistically significant (p for interaction, 0.012). Multivariable-adjusted and propensity score-adjusted associations of ARB (versus ACEI) use and all-cause mortality in the 4044 pre-match patients are displayed in Table 2.

HF hospitalization occurred in 59% and 61% of matched patients receiving ARBs and ACEIs respectively (HR associated with ARB use, 0.99; 95% CI, 0.86–1.14; p=0.876). HRs for HF hospitalization associated with ARB (versus ACEI) use were 0.80 (95% CI, 0.63–1.03; p=0.080) and 1.14 (95% CI, 0.91–1.43; p=0.246) among matched HF patients with LVEF $\geq$ 45% and LVEF <45%, respectively (p for interaction, 0.060). All-cause hospitalization occurred in 89% and 87% of matched patients receiving ARBs and receiving ACEIs at discharge (HR associated with ARB use, 1.07; 95% CI, 0.96–1.21; P=0.226). HRs for all-cause hospitalization associated with ARB (versus ACEI) use were 0.90 (95% CI, 0.74–1.11; p=0.341) and 1.24 (95% CI, 1.03–1.49; p=0.021) among matched patients with LVEF $\geq$ 45% and LVEF <45%, respectively (p for interaction, 0.039).

Discussion

Findings from the current propensity-matched comparative effectiveness research demonstrate that older HF patients discharged with prescriptions of ARBs (versus ACEIs) had lower all-cause mortality. This association was independent of 56 baseline demographic, clinical, subclinical, and biochemical characteristics, and was primarily driven by a greater mortality reduction in those with HF-PEF. Although ARB use had no significant association with hospitalizations overall, there was a trend for lower HF hospitalization among those

with HF-PEF and there was significant increased risk of all-cause hospitalization among those with systolic HF. To the best of our knowledge this is the first report of a comparative effectiveness research of ACEIs versus ARBs in a cohort of propensity-matched real world HF patients.

The lack of a significant difference in mortality and HF hospitalization between HF-REF patients receiving ACEIs versus ARBs is consistent with findings from RCTs.²³ During chronic therapy with ACEIs angiotensin II may be produced via ACE-independent chymase-mediated pathways that are not suppressed by ACEIs.^{24, 25} Because ARBs inhibits the actions of angiotensin II at the receptor level these drugs were expected to provide a more complete RAS blockade and better clinical outcomes. The clinical benefits of ACEIs despite an incomplete RAS blockade suggest that the effects of ACEIs are mediated via mechanisms other than RAS suppression, including potentiating the effect of bradykinin, a cardioprotective vasodilator. The cardioprotective effects of ACEIs have been shown to be mediated via activation of B2-type bradykinin receptors through which most of the cardioprotective effects of bradykinin are mediated.²⁶ Whether age-related changes in the bradykinin B2-type receptors may alter this balance in favor of ARBs remain unknown. Findings from laboratory animals suggest that expression of bradykinin B2-type receptors is reduced in older rat myocardium.²⁷ The increased risk of overall hospitalization in those with systolic HF is intriguing. However, the small number of events for non-HF hospitalizations precluded further analysis by cause-specific hospitalization.

The mortality reduction associated with ARB use in HF-PEF patients is intriguing as ARBs have not reduced mortality in large RCTs of HF-PEF.^{28, 29} This may in part be explained by the differences in patient characteristics between trial-eligible younger patients and older hospitalized real-world HF patients in the current analysis. It has been suggested that unlike ACEIs, ARBs may not have a class effect and in one recent study, HF-PEF patients receiving candesartan had lower mortality than those receiving losartan.³⁰ However, the vast majority of patients receiving ARBs in our study received losartan. It is also possible that older HF-PEF patients prescribed ACEIs were more non-adherent to those drugs due to side effects such as cough, which may overestimate the benefits of ARBs. Finally, bias by indication is possible.³¹ However, the guidelines recommend the use of ACEIs (over ARBs) in HF-REF, not in those with HF-PEF,^{1, 3} and thus any bias by indication would likely be minimal. Whether the reduction in the expression of bradykinin B2-type receptors observed in older rats may be exaggerated in those with normal LVEF remains unclear.²⁷ However, given the small sample size of the HF-PEF patients, chance remains a potential explanation. Therefore, the findings of the current analysis need to be replicated in larger cohorts of HF patients such as the as the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry.²²

Our study has several limitations. Bias due to unmeasured confounding is possible but unlikely given the findings of our sensitivity analysis. Further, sensitivity analyses cannot determine whether such unmeasured confounders exist or not. In addition to being a near-perfect predictor of death and increasing the odds of ARB use by nearly 8%, a hidden covariate could not be strongly correlated with any of the 56 baseline characteristics used in our study, which is an unlikely possibility. In conclusion, our observation of a significant reduced mortality and a trend toward reduced HF hospitalization in older HF-PEF patients receiving ARBs (versus ACEIs) is intriguing and hypothesis generating, and needs to be replicated in other larger propensity-matched HF populations.

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Figure 1.

Absolute standardized differences for 56 baseline characteristics between older HF patients receiving discharge prescriptions of angiotensin-converting enzyme inhibitors versus angiotensin receptors blockers, before and after propensity score matching. AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; NSAID = nonsteroidal anti inflammatory drug; PCI = percutaneous coronary intervention.

Figure 2.

Kaplan-Meier plots for all-cause mortality in a propensity-matched cohort of older heart failure patients receiving discharge prescription of angiotensin-converting enzyme inhibitors (ACEIs) versus angiotensin receptor blockers (ARBs), data from (a) all patients, and those with left ventricular ejection fraction (LVEF) (b) $\geq 45\%$ and (c) $< 45\%$

Table 1

Baseline patient characteristics of older heart failure patients receiving prescriptions of angiotensin receptor blockers (ARBs) versus angiotensin-converting enzyme inhibitors (ACEIs) during hospital discharge, before and after propensity score matching

n (%) or mean ($\pm$ SD)	Pre-match		Post-match	
	ACEIs (n=3383)	ARBs (n=661)	ACEIs (n=655)	ARBs (n=655)
		P value		P value
Age (years)	78 ($\pm$ 8)	78 ($\pm$ 7)	78 ($\pm$ 8)	78 ($\pm$ 7)
Female	1994 (59%)	461 (70%)	452 (69%)	455 (70%)
African American	770 (23%)	133 (20%)	115 (18%)	133 (20%)
Current smoker	314 (10%)	38 (6%)	33 (5%)	38 (6%)
Nursing home residents	214 (6%)	28 (4%)	27 (4%)	28 (4%)
Past medical history				
Prior heart failure	2470 (73%)	477 (72%)	491 (75%)	474 (72%)
Hypertension	2436 (72%)	516 (78%)	510 (78%)	510 (78%)
Coronary artery disease	1851 (55%)	387 (59%)	370 (57%)	381 (58%)
Percutaneous coronary intervention	407 (12%)	133 (20%)	132 (20%)	128 (20%)
Coronary artery bypass graft	793 (23%)	191 (29%)	186 (28%)	187 (29%)
Diabetes mellitus	1456 (43%)	290 (44%)	286 (44%)	287 (44%)
Atrial fibrillation	995 (29%)	159 (24%)	157 (24%)	158 (24%)
Dementia	319 (9%)	42 (6%)	44 (7%)	42 (6%)
Cancer	76 (2%)	16 (2%)	10 (2%)	16 (1%)
Clinical findings				
Pulse (beats per minute)	89 ($\pm$ 23)	86 ($\pm$ 22)	86 ($\pm$ 21)	86 ($\pm$ 22)
Systolic blood pressure (mmHg)	152 ($\pm$ 32)	152 ($\pm$ 31)	153 ($\pm$ 31)	152 ($\pm$ 31)
Diastolic blood pressure (mmHg)	81 ($\pm$ 19)	79 ($\pm$ 19)	79 ($\pm$ 18)	79 ($\pm$ 19)
Respiration (breaths per minute)	24 ($\pm$ 6)	23 ($\pm$ 6)	23 ($\pm$ 6)	23 ($\pm$ 6)
Peripheral edema	2341 (69%)	473 (72%)	463 (71%)	467 (71%)
Pulmonary edema by chest x-ray	2348 (69%)	418 (63%)	421 (64%)	415 (63%)
Laboratory data				
Serum sodium (mEq/L)	139 ($\pm$ 5)	139 ($\pm$ 5)	138 ($\pm$ 5)	138 ($\pm$ 5)
Serum potassium (mEq/L)	4.3 ($\pm$ 0.6)	4.2 ($\pm$ 0.6)	4.3 ($\pm$ 0.7)	4.2 ($\pm$ 0.6)

n (%) or mean (±SD)	Pre-match		Post-match	
	ACEIs (n=3383)	ARBs (n=661)	ACEIs (n=655)	ARBs (n=655)
			P value	P value
Serum creatinine (mEq/L)	1.4 (±0.9)	1.5 (±0.9)	0.029	1.5 (±0.9)
Estimated glomerular filtration rate (ml/min/1.73m ²)	57 (±26)	51 (±20)	<0.001	51 (±20)
Blood urea nitrogen (mg/dL)	25 (±14)	27 (±15)	0.001	27 (±15)
Serum glucose (mg/dL)	152 (±69)	149 (±68)	0.371	149 (±68)
Hematocrit (%)	37 (±6)	36 (±6)	0.005	36 (±6)
White blood cell (10 ³ /uL)	9 (±5)	9 (±4)	0.345	9 (±4)
Left ventricular ejection fraction				
<45%	1477 (44%)	257 (39%)		282 (43%)
>45%	967 (28%)	221 (33%)	0.025	201 (31%)
Unknown	939 (28%)	183 (28%)		172 (26%)
Hospital and care characteristics				
Incident pneumonia	837 (25%)	142 (22%)	0.074	152 (23%)
Incident acute myocardial infarction	139 (4%)	19 (3%)	0.134	17 (3%)
Incident pressures ulcer	253 (8%)	48 (7%)	0.846	47 (7%)
Rural hospital	1108 (33%)	165 (25%)	<0.001	160 (24%)
Cardiology consult	1815 (54%)	372 (57%)	0.215	359 (55%)
Intensive care unit	96 (3%)	34 (5%)	0.002	31 (5%)
Length of stay (days)	6 (±5)	6 (±4)	0.380	6.3 (±4.3)
Discharge medications				
Beta blockers (heart failure)	774 (23%)	160 (24%)	0.459	162 (25%)
Loop diuretics	2961 (88%)	576 (87%)	0.784	574 (88%)
Digoxin	1729 (51%)	228 (44%)	<0.001	293 (45%)
Potassium-sparing diuretics	542 (16%)	112 (17%)	0.556	102 (16%)
Potassium supplements	1629 (48%)	347 (53%)	0.041	354 (54%)
				343 (52%)
				0.542

Table 2

Association of prescriptions of angiotensin receptor blockers (ARBs) versus angiotensin-converting enzyme inhibitors (ACEIs) with all-cause mortality in older HF patients

	% (events/ total)		Absolute risk difference* (%)	Hazard ratio † (95% confidence interval)	P value
	ACEIs	ARBs			
Pre-match unadjusted	67% (2258/3383)	63% (413/661)	−4	0.87 (0.78–0.97)	0.009
Pre-match multivariable-adjusted	---	---		0.90 (0.81–1.00)	0.051
Pre-match propensity-adjusted	---	---		0.91 (0.81–1.01)	0.069
Post-match	68% (446/655)	63% (410/655)	−5	0.86 (0.75–0.99)	0.031

* Absolute risk differences were calculated by subtracting percent events in patients receiving ACEIs from those receiving ARBs

† Hazard ratios comparing patients receiving ARBs versus those receiving ACEIs