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Renin-angiotensin inhibition and outcomes in nursing home residents with heart failure

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Abstract

Background: Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEIs-ARBs) improve outcomes in heart failure (HF). Less is known about this association in nursing home (NH) residents.

Study Question: Evaluate the association of ACEIs or ARBs with outcomes in NH residents hospitalized for HF.

Study Design: Propensity score-matched cohort study of NH residents hospitalized for HF receiving and not receiving ACEIs-ARBs and subsequent outcomes.

Methods and Outcomes: Of the 8024 hospitalized HF patients, 542 were NH residents, of which 252 received ACEIs-ARBs. We assembled a propensity score-matched cohort of 157 pairs of NH residents receiving and not receiving ACEIs-ARBs balanced on 29 baseline characteristics (mean age, 3 years, 74% women, 17% African American), in which we estimated hazard ratios (HR) and 95% confidence intervals (CI) for 30-day all-cause readmission, HF readmission and

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all-cause mortality associated with ACEI-ARB use. We then checked for interaction in a matched cohort of 5130 patients (378 were NH residents) assembled form 8024 patients.

Results: Among 314 matched NH residents, HRs (95% CIs) for 30-day all-cause readmission, HF readmission and all-cause mortality were 0.78 (0.47–1.28), 0.68 (0.29–1.60) and 1.26 (0.70–2.27), respectively. Respective HRs (95% CIs) at 1 year were 0.76 (0.56–1.02), 0.68 (0.42–1.09) and 1.04 (0.78–1.38). Among 5130 matched patients, ACEI-ARB use was associated with a significantly lower risk of all outcomes at both times, with no significant interactions, except for 1-year mortality (p for interaction, 0.026).

Conclusions: We found no evidence that the use of ACEIs or ARBs is associated with improved outcomes in patients with HF in the NH setting. However, we also found on evidence that this association is different in NH residents with HF versus other HF patients. Future larger studies are needed to demonstrate effectiveness of these drugs in the NH setting.

Keywords

ACEIs; ARBs; nursing home; heart failure; mortality; readmission

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been shown to be associated with better outcomes in patients with heart failure and reduced ejection fraction (HFrEF).¹ HF is associated with poor outcomes and a leading cause for hospital readmission in older Medicare beneficiaries.² We have previously demonstrated that a discharge prescription for ACEIs or ARBs may reduce the risk for readmission in these patients.³ Nursing home (NH) residents hospitalized for HF are characteristically and prognostically different from those HF patients living in the communities.^{4,5} In the current analysis, we examined the association of a discharge prescription of ACEIs or ARBs with outcomes in NH residents hospitalized for HF.

Methods

Data source and study patients

The Alabama Heart Failure Project (AHFP) is a HF registry, the details of which have been previously described.^{6–8} Charts of 8555 unique fee-for-service Medicare beneficiaries who had primary discharge diagnoses codes for HF were abstracted by trained data abstractors using structured data collection tools.⁶ These patients were discharged from 106 Alabama hospitals between 1998 and 2001, and of these 545 (7%) were NH residents. Data on demographics and other baseline characteristics, medication use, and in-hospital care were centrally collected by trained chart abstractors.⁶

Discharge prescription for ACEIs or ARBs

Data on the receipt of ACEIs or ARBs were collected by chart abstraction. Of the 545 patients admitted from a NH, 3 had a history of intolerance to ACEIs and were excluded. Of the remaining 542 patients, 250 received discharge prescriptions for ACEIs or ARBs (Figure 1). Given the small sample size, we did not restrict our analysis to an inception cohort or those with reduced ejection fraction.

Outcomes

We examined all-cause readmission, HF readmission, all-cause mortality, and the combined end point of all-cause readmission or all-cause mortality at 30 days and 1 year. Data on all outcome variables were obtained from the CMS Medicare data.^{6,9,10}

Assembly of a balanced cohort: Propensity score matching

Because patients were not randomly prescribed ACEIs or ARBs, to minimize indication bias, we used propensity scores for the receipt of ACEIs or ARBs to assemble a matched cohort of patients in which those receiving and not receiving these drugs would be balanced on key measured baseline characteristics.^{11,12} A non-parsimonious multivariable logistic regression model was used to estimate propensity scores for the receipt of ACEIs or ARBs for each of the 542 patients. The model was adjusted for 29 baseline characteristics presented in Figure 1. We then used the propensity scores to assemble a matched cohort of 157 pairs of patients receiving and not receiving ACEIs or ARBs (Figure 1). Absolute standardized differences were estimated to assess post-match balance, with 0% indicating no residual bias and <10% inconsequential bias.¹³

Test of interaction

To examine if the lack of association of ACEI or ARB use with outcomes in NH residents was significantly different from that among non-NH residents, we repeated the above process in 8024 patients with no history of intolerance to ACEIs, of which 4735 received discharge prescriptions for ACEIs or ARBs (Figure 1). From these patients, we assembled a matched cohort of 5130 patients, of which 2565 were receiving ACEIs or ARBs, and 378 were NH residents (Figure 1).

Assembly of a sensitivity cohort

The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) is a large national HF registry, which has been described previously.^{14,15} The current analysis is based on the Medicare-linked OPTIMZE-HF that included 26,376 unique patients discharged from 259 hospitals in 48 states during 2003–2004 with a primary discharge diagnosis of HF. Of these, 471 were NH residents. Because of the small number of NH residents in the OPTIMIZE-HF, we used data from the AHFP for our primary analyses. Furthermore, AHFP have data on variables considered prognostically important in the NH setting such as dementia and pressure ulcer that are not available in OPTIMIZE-HF. Thus, for our sensitivity analysis, we merged the 545 NH residents from AHFP described above with the 471 NH residents from OPTIMIZE-HF to assemble a merged cohort of 1016 NH residents, of whom 483 were receiving ACEIs or ARBs. From the merged data, we were able to identify 23 baseline characteristics that were common to both datasets. Using approaches described above, we assembled a propensity score-matched cohort of 734 patients balanced on these 23 baseline characteristics.

Statistical analysis

For descriptive analyses comparing between-group baseline characteristics, we used Pearson's Chi-square and Wilcoxon rank-sum tests as appropriate. All associations between

the use of ACEIs or ARBs and outcomes were examined in the matched cohort using Cox regression models. Kaplan-Meier survival analyses were used to plot the combined end point of all-cause hospital readmission or all-cause mortality at 12 months. All statistical tests were two-tailed with a p-value <0.05 considered significant. SPSS for Windows version 24 (IBM Corp., Armonk, NY) were used for data analyses.

Results

Baseline characteristics

Matched patients (n=314) had a mean age of 83 (\pm 8) years, 74% were women and 17% were African American. Before matching, more patients receiving ACEIs or ARBs had a lower mean EF and serum creatinine, and were receiving beta-blockers, digoxin and diuretics. However, these and other imbalances were balanced after matching (Table 1 and Figure 2).

30-day outcomes in propensity score-matched NH residents

Among the 314 propensity score-matched NH residents with HF in the AHFP, the combined end point of 30-day all-cause readmission or 30-day all-cause mortality occurred in 31% (48/157) and 34% (54/157) of matched patients receiving and not receiving a discharge prescription for ACEIs or ARBs, respectively (hazard ratio {HR} when the use of ACEIs or ARBs was compared with their non-use, 0.86; 95% confidence interval {CI}, 0.58–1.27; Table 2 and Figure 3). There was no association with other 30-day outcomes (Table 2).

12-month outcomes in propensity score-matched NH residents

Among the 314 propensity score-matched NH residents with HF in the AHFP, the combined end point of 1-year all-cause readmission or 1-year all-cause mortality occurred in 82% (129/157) and 89% (139/157) of matched patients receiving and not receiving a discharge prescription for ACEIs or ARBs, respectively (HR associated with ACEI or ARB use, 0.84; 95% CI, 0.66–1.06; Table 3 and Figure 3). Use of ACEIs or ARBs was not associated with other 1-year outcomes (Table 3).

Findings from the interaction tests

Among the 5130 propensity score-matched patients with HF in the AHFP, the use of ACEIs or ARBs was associated with a significantly lower risk of all all-cause readmission, HF readmission, and all-cause mortality at 30 days and 1 year (Figure 4). All associations were significant in the non-NH resident subset of patients and none of the association was significant among NH residents. However, none of these differences were statistically significant except for 1-year all-cause mortality (p for interaction, 0.026; Figure 4).

Findings from the sensitivity cohort

Among the 734 propensity score-matched NH residents with HF in the combined AHFP and OPTIMIZE-HF datasets, the use of ACEIs or ARBs was not associated with any outcomes at 30 days and 1 year (Tables 2 and 3).

Discussion

Findings from our study demonstrate that there is no evidence that the clinical effectiveness of ACEIs or ARBs in patients with HF varied between NH and non-HF residents. However, our findings also did not reveal that the use of these drugs was associated with improved outcomes in NH residents hospitalized for HF, likely due to small sample size. Considering the lack of power and the fact NH residents are heterogeneous with many competing risks for poor outcomes, these findings need to be interpreted with caution.

ACEIs and ARBs have little effect on sudden cardiac death, one of the more common modes of death in HF, and instead improve outcomes by reducing the risk of hospitalization and death due to progressive pump failure.¹⁶ This is important as pump failure death is a relatively more common mode of death in patients with more advanced HF and older NH residents with HF would be expected to have more advanced HF.^{17–19} Yet, we observed that the use of these drugs had no association with any outcomes in NH residents. One potential explanation for the lack of association of ACEI or ARB use with outcomes in these patients is the high burden of non-cardiovascular morbidity. Most of the morbidity and mortality in older NH residents are due to non-cardiovascular causes, which may help explain why these drugs may not be effective in improving outcomes. Further, our inclusion of patients with HF with preserved ejection fraction may have further attenuated any beneficial association between ACEIs or ARBs with outcomes. Finally, hospitalized NH residents may have a high mortality rate,²⁰ which may in part result in a survivor cohort that may be at a lower risk for poor outcomes and be less responsive to the beneficial effects of ACEIs and ARBs.

Several studies have reported underutilization of ACEIs in the NH settings.^{21–24} However, there is little evidence from the literature that demonstrate the clinical effectiveness of ACEIs or ARBs in older NH residents with HF.^{25–27} Findings from our study have important implications. If our results can be replicated in a prospective study with a more contemporary cohort of NH residents with HF, this may help reduce the polypharmacy burden in this population. In contrast, if evidence of their clinical effectiveness can be demonstrated, strategies may need to be developed and tested to achieve their optimal underutilization. Further, more recent evidence suggests the superiority of angiotensin receptor neprilysin inhibitors over ACEIs in HFrEF and these benefits may extend to patients age 75 years of age and older.²⁸ Studies evaluating the clinical effectiveness of these agents in NH residents are needed.

Our study has several limitations. Despite our use of propensity score-matching, bias due to residual confounding or unmeasured confounding such as physical function and patient and family preference is possible. We had considered formal sensitivity analyses but it was not necessary due to the observed null associations. Lack of power and chance are other possibilities given our small sample size. We had no data on post-discharge adherence and crossover of treatment during follow-up and regression dilution may in part explain a null association. Finally, findings of this study based on fee-for-service Medicare beneficiaries from one state from an earlier era of HF therapy may limit generalizability. However, treatment of HF in NH residents has not changed much in the past two decades.

In conclusion, we found no evidence of clinical effectiveness of ACEIs or ARBs in patients with HF in the NH setting. However, we also found no evidence that this association is significantly different between NH residents with HF versus other HF patients. These negative findings, from two relatively large HF registries, albeit with a small subset of NH residents, would need to be interpreted with caution due the modest sample size. Taken together, these findings suggest, future sufficiently powered studies are needed to establish evidence of clinical effectiveness of ACEIs or ARBs in patients with HF in the NH setting.

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Primary analyses cohort

Interaction analysis cohorts

Figure 1.

Flow chart displaying (1) assembly of a propensity score-matched cohorts of nursing home (NH) residents hospitalized for heart failure by receipt of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) and (2) assembly of a propensity score matched cohort of all patients hospitalized for heart failure, by receipt of ACEIs or ARBs, stratified into NH and non-NH residents



Figure 2.

Love plot displaying absolute standardized differences for 29 baseline characteristics between patients receiving and not receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, before and after propensity score matching

Overall HR, =0.84; 95% CI=0.66-1.06; p=0.147



Figure 3.

Kaplan-Meier plots for the combined end point of all-cause hospital readmission or allcause mortality in a propensity-matched cohort of older heart failure patients admitted from nursing homes receiving and not receiving a discharge prescription for angiotensinconverting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) (HR=hazard ratio; CI=confidence interval)

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	ACEI or ARB use			Hazard ratio	P value	P value
	No	Yes		(95% CI)	Effect	Interaction
30-day outcomes				c 5		
All-cause readmission			1			
Non-NH residents (n=4752)	571/2375 (24)	468/2377 (20)	HI I	0.79 (0.70-0.89)	< 0.001	0.716
NH residents (n=378)	47/190 (25)	36/188 (19)		0.73 (0.47-1.23)	0.156	0.710
Overall (N=5130)	618/2565 (24)	504/2565 (20)	⊢∎ -1 [0.79 (0.70-0.89)	< 0.001	
HF readmission						
Non-NH residents (n=4752)	243/2375 (10)	154/2377 (7)	⊢◆┤	0.72 (0.50-0.75)	< 0.001	0.270
NH residents (n=378)	18/190 (10)	7/188 (4)		0.38 (0.16-0.91)	0.029	0.279
Overall (N=5130)	261/2565 (10)	161/2565 (6)	H=-1	0.60 (0.49-0.73)	< 0.001	
All-cause mortality						
Non-NH residents (n=4752)	157/2375 (7)	98/2377 (3)		0.62 (0.48-0.79)	< 0.001	0.004
NH residents (n=378)	31/190 (16)	26/188 (14)		0.84 (0.50-1.41)	0.505	0.301
Overall (N=5130)	188/2565 (7)	124/2565 (5)		0.62 (0.48-0.79)	< 0.001	
1-year outcomes						
All-cause readmission						
Non-NH residents (n=4752)	1645/2375 (69)	1558/2377 (66)	H I	0.85 (0.79-0.91)	< 0.001	0.942
NH residents (n=378)	123/190 (65)	107/188 (57)		0.84 (0.65-1.09)	0.181	
Overall (N=5130)	1768/2565 (69)	1665/2565 (65)	∎	0.85 (0.79-0.91)	<0.001	
HF readmission						
Non-NH residents (n=4752)	815/2375 (34)	732/2377 (31)	H+H	0.83 (0.75-0.92)	< 0.001	0.745
NH residents (n=378)	47/190 (25)	35/188 (19)		0.77 (0.49-1.19)	0.231	
Overall (N=5130)	862/2565 (34)	767/2565 (30)	H=-1	0.83 (0.75-0.91)	< 0.001	
All-cause mortality			8			
Non-NH residents (n=4752)	820/2375 (35)	689/2377 (29)	H+H I	0.80 (0.72-0.89)	< 0.001	0.026
NH residents (n=378)	116/190 (61)	120/188 (64)	⊢ ;♦ – –	1.09 (0.84-1.41)	0.511	
Overall (N=5130)	936/2565 (37)	806/2565 (32)	HeH	0.83 (0.75–0.91)	<0.001	
	Events / at risk (%)		.2 .4 .6 .8 1.0 1.2 1.4			
			HR (95% CI)			

Figure 4.

Hazard ratios and 95% confidence intervals (CI) for outcomes by use of angiotensinconverting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) in propensity score-matched patients with heart failure, and subgroups of nursing homes (NH) residents versus other patients

Table 1

Baseline characteristics of nursing home resident Medicare beneficiaries hospitalized for decompensated heart failure, by the receipt of a discharge prescription for angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), before and after propensity score matching

	Pre-match (N=542)			Post-match (N=314)		
n (%) or mean (±SD)	Use of ACE inhibitors or ARBs			Use of ACE inhibitors or ARBs		
	No (n=292)	Yes (n=250)	P value	No (n=157)	Yes (n=157)	P value
Age (years)	83 (±8)	83 (±9)	0.978	83 (±8)	83 (±9)	0.801
Female	211 (72%)	192 (77%)	0.228	115 (73%)	117 (75%)	0.797
African American	52 (18%)	50 (20%)	0.515	27 (17%)	26 (17%)	0.880
Current smoker	15 (5%)	11 (4%)	0.689	10 (6%)	6 (4%)	0.305
LVEF < 45%	42 (14%)	79 (32%)	< 0.001	37(24%)	31 (20%)	0.411
Past medical history						
History of heart failure	214 (73%)	198 (79%)	0.108	126 (80%)	125 (80%)	0.888
Hypertension	192 (66%)	183 (73%)	0.061	110 (70%)	112 (71%)	0.804
Coronary artery disease	129 (44%)	119 (48%)	0.425	73 (47%)	76 (48%)	0.735
Diabetes mellitus	117 (40%)	120 (48%)	0.064	70 (45%)	66 (42%)	0.649
Atrial fibrillation	75 (26%)	80 (32%)	0.105	47 (30%)	46 (29%)	0.902
Stroke	116 (40%)	93 (37%)	0.547	67 (43%)	58 (37%)	0.299
Chronic obstructive pulmonary disease	119 (41%)	74 (30%)	0.007	60 (38%)	59 (38%)	0.907
Dementia	143 (49%)	108 (43%)	0.179	69 (44%)	70 (45%)	0.910
Clinical findings						
Pulse (beats per minute)	93 (±24)	90 (±22)	0.093	92 (±24)	91 (±23)	0.767
Systolic blood pressure (mmHg)	143 (±30)	146 (±33)	0.230	146(±30)	144 (±33)	0.595
Pulmonary edema by chest x-ray	246 (84%)	207 (83%)	0.650	136 (87%)	134(85%)	0.745
Laboratory values						
Serum creatinine (mg/dL)	1.6 (±1.1)	1.3 (±0.7)	0.003	1.4 (±0.7)	1.4 (±0.8)	0.671
In-hospital events						
Pneumonia (any)	134 (46%)	108 (43%)	0.530	71 (45%)	71 (45%)	1.000
Acute myocardial infarction	15 (5%)	13 (5%)	0.974	9 (6%)	10 (6%)	0.813
Pressure ulcer	84 (29%)	62 (25%)	0.299	41 (26%)	38 (24%)	0.696
Hospital and care characteristics						
Rural hospital	109 (37%)	105 (42%)	0.267	66 (42%)	63 (40%)	0.731
Cardiology consult	93 (32%)	82 (33%)	0.813	56 (36%)	52 (33%)	0.635
Intensive care unit	10 (3%)	8 (3%)	0.884	6 (4%)	3 (2%)	0.310
Length of stay (days)	7 (±5)	7 (±6)	0.893	7 (±5)	8 (±6)	0.528
Discharge medications						
Beta-blockers	43 (15%)	64 (26%)	0.002	35 (22%)	34 (22%)	0.892
Digoxin	100 (34%)	126 (50%)	< 0.001	69 (44%)	68 (43%)	0.909
Loop diuretics	208 (71%)	221 (88%)	< 0.001	130 (83%)	130 (83%)	1.000
Potassium-sparing diuretics	23 (8%)	41 (16%)	0.002	16 (10%)	19 (12%)	0.591
Potassium supplements	124 (43%)	114 (46%)	0.464	68 (43%)	53 (48%)	0.365

Table 2 and Table 3

Association between a discharge prescription for angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and post-discharge outcomes in a propensity-matched cohorts of nursing home resident Medicare beneficiaries hospitalized for decompensated heart failure

20 1	% (events) Use of ACEIs or ARBs		*	Hazard ratio [†] (95% confidence interval)	
30-day outcomes			Absolute risk difference		
AHFP Cohort	No (n=157)	Yes (n=157)			
<u>30-day outcomes</u>					
All-cause readmission	22% (35)	18% (28)	-4%	0.78 (0.47–1.28)	
Heart failure readmission	8% (13)	6% (9)	-2%	0.68 (0.29–1.60)	
All-cause mortality	13% (20)	16% (25)	+3%	1.26 (0.70–2.27)	
All-cause mortality or all-cause readmission	34% (54)	31% (48)	-3%	0.86 (0.58–1.27)	
1-year outcomes					
All-cause readmission	62% (97)	52% (82)	-10%	0.76 (0.56-1.02)	
Heart failure readmission	27% (42)	18% (28)	-9%	0.68 (0.42-1.09)	
All-cause mortality	62% (97)	61% (96)	-1%	1.04 (0.78–1.38)	
All-cause mortality or all-cause readmission	89% (139)	82% (129)	-7%	0.84 (0.66–1.06)	
AHFP + OPTIMIZE-HF Cohorts	No (n=367)	Yes (n=367)			
30-day outcomes					
All-cause readmission	24% (87)	23% (84)	-1%	0.94 (0.70–1.27)	
Heart failure readmission	8% (28)	7% (26)	-1%	0.92 (0.54–1.57)	
All-cause mortality	16% (58)	14% (52)	-2%	0.89 (0.61–1.30)	
All-cause mortality or all-cause readmission	35% (130)	33% (121)	-2%	0.91 (0.71–1.16)	
1-year outcomes					
All-cause readmission	64% (235)	63% (230)	-1%	0.95 (0.79–1.14)	
Heart failure readmission	26% (97)	25% (91)	-1%	0.94 (0.71–1.25)	
All-cause mortality	60% (97)	60% (96)	0%	0.99 (0.82–1.19)	
All-cause mortality or all-cause readmission	87% (319)	86% (315)	-1%	0.96 (0.82-1.12)	

Absolute risk differences were calculated by subtracting percent events in patients receiving no ACEIs or ARBs from those receiving those drugs

[†]The hazard ratios compared patients receiving ACEIs or ARBs versus those not receiving those drugs. These hazard ratios were calculated by treating patients without events during the first 30 days as censored.