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Effectiveness of sacubitril/valsartan versus aldosterone antagonists in heart failure with reduced ejection fraction: A retrospective cohort study

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Abstract

Study Objective: To assess the effectiveness of sacubitril/valsartan versus angiotensin receptor antagonist therapy for prevention of heart failure (HF)-related hospitalization and all-cause hospitalization in a large cohort of patients with heart failure with reduced ejection fraction (HFrEF).

Design: Retrospective cohort study.

Data Source: IBM® MarketScan® research databases (2014–2018).

Patients: Patients aged 18 years or older with their first HFrEF hospitalization on or after January 1, 2015, who initiated sacubitril/valsartan or angiotensin receptor antagonist after hospital discharge.

Intervention: Sacubitril/Valsartan versus Angiotensin receptor antagonist.

Measurements and Main Results: The index date was the first sacubitril/valsartan or angiotensin receptor antagonist fill date. After 1 up to 3 propensity score matching, Cox proportional hazards regression was used with robust variance estimators to compare HF-related and all-cause hospitalizations between treatments. Subgroup and sensitivity analyses were conducted to assess the robustness of the main analysis. After propensity score matching, 1,088 sacubitril/valsartan and 2,839 angiotensin receptor antagonist new users were included. The crude incidence of HF-related hospitalization was 13 per 100 person-years for sacubitril/valsartan users and 18 per 100 person-years for angiotensin receptor antagonist users. Compared with angiotensin receptor antagonist use, sacubitril/valsartan use was associated with 27% lower risk of HF-related hospitalization (adjusted hazard ratio, 0.73; 95% confidence interval, 0.58–0.91; $p = 0.006$) and 31% lower risk of all-cause hospitalization (adjusted hazard ratio, 0.69; 95% confidence interval, 0.61–0.79; $p < 0.001$). Subgroup analyses revealed no significant heterogeneity, including subpopulations with chronic kidney disease or coronary artery disease.

Conclusions: Compared with angiotensin receptor antagonists, sacubitril/valsartan was associated with lower risk of HF-related and all-cause hospitalizations. Our data suggest that, when added sequentially, sacubitril/valsartan should be the preferred initial agent over angiotensin receptor antagonists.

KEYWORDS
all-cause hospitalization, angiotensin receptor-neprilysin inhibitor, HF-related hospitalization, real-world evidence, sacubitril/valsartan

1 | INTRODUCTION

In the United States (US), 6.2 million adults have heart failure (HF), and more than a million HF-related hospitalizations occur annually. Half of these hospitalizations are due to HF with reduced ejection fraction (HFrEF).[1] Despite significant advances in HF management, morbidity and mortality remain high. Angiotensin-converting enzyme inhibitors (ACEIs) and β-blockers have been the cornerstone of treatment for HF since they were shown to reduce mortality in patients with HFrEF.[2,3] In 2015, sacubitril/valsartan (SAC/VAL), a first-in-class angiotensin receptor-neprilysin inhibitor, was approved by the US Food and Drug Administration for management of HFrEF. Evidence from multicenter randomized clinical trials (RCTs) has shown superior efficacy of SAC/VAL in lowering risks of mortality and HF-related hospitalization compared with the ACEI enalapril.[4,5] Most importantly, PARADIGM-HF has shown that patients receiving SAC/VAL have 20% lower risk of cardiovascular death or HF-related hospitalization than those receiving enalapril.[4]

Aldosterone antagonists (ARAs) are also recommended for HFrEF given that aldosterone plays a vital part in the pathophysiology of HF by promoting myocardial fibrosis and decreasing norepinephrine reuptake in addition to its electrolyte and metabolic effects.[6] Several RCTs have demonstrated the efficacy of ARAs when added to standard therapy (ie, ACEI/ARB, diuretic, and β-blocker) to reduce mortality and HF-related hospitalization among patients with HFrEF.[7,8] A subsequent meta-analysis of RCTs determined that additional use of an ARA with an ACEI/ARB and a β-blocker combined reduces re-hospitalization due to HF or cardiac causes among patients with mild-to-moderate HFrEF.[9] Observational studies have also found a protective effect of ARA use on the risk of HF-related readmissions among older patients with HFrEF.[9,10]

SAC/VAL and ARA were each recommended Step 2 therapies by American Heart Association 2017 guidelines during a portion of the time period analyzed in this study.[11] Recently, SAC/VAL has been recommended as first-line therapy for patients with HFrEF by the 2021 report of the American College of Cardiology (ACC) Solution Set Oversight Committee even for those who are already on ACEI or ARB.[12] However, the question whether ARA should be added prior to SAC/VAL initiation or not still remains unanswered because of little data on order of initiation. To date, there are no direct comparisons of SAC/VAL and ARAs. Thus, we aimed to assess the effectiveness of SAC/VAL versus ARA therapy for prevention of HF-related hospitalization and all-cause hospitalization in a large cohort of patients with HFrEF.

2 | METHODS

2.1 | Study design and data source

We conducted a retrospective cohort study using IBM® MarketScan® research databases, from January 1, 2014, to December 31, 2018. The databases contain de-identified patient-level medical and pharmacy claims data of nearly 70 million individuals annually. Data are contributed by large employers, managed care organizations, hospitals, electronic medical records providers, and Medicare. The commercial and Medicare supplemental databases contain the healthcare experience of individuals in the United States with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service, or capitated health plans. This study was approved by the University of Florida Institutional Review Board.

2.2 | Study population

Patients aged ≥18 years were included on their first HFrEF hospital admission on or after January 1, 2015, with a primary or secondary diagnosis of HFrEF in inpatient admission claims, and if they had no other HF-related hospital admission in the preceding 12 months. *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* (*ICD-9-CM*) codes (428.2x) and *ICD-10-CM* (I50.2x) codes,[13,14] were used to identify HFrEF. Patients were required to be new users of an ARA (spironolactone or eplerenone) or SAC/VAL within 180 days of the hospital discharge date of the first HFrEF admission. They were also required to have continuous enrollment in their health plan for the 12 months prior to HFrEF admission and through treatment initiation. The treatment initiation date of SAC/VAL or ARA was considered the index date (Figure S1).

2.3 | Study outcomes

The primary study outcome was an HF-related hospital readmission, defined as a primary hospital discharge diagnosis for HF, using the previously validated *ICD-9-CM* codes 402.x1, 404.x1, 404.x3, and 428.xx and *ICD-10-CM* codes I11.0, I13.0, I13.2, I50.1, I50.2, I50.3, I50.4, and I50.9 with positive predictive values (PPVs) in the range of 80%–97%.[15,16] The secondary outcome was all-cause hospitalization. Patient follow-up occurred, separately for HF-related and all-cause hospitalization, from the index date to first occurrence of an outcome, treatment discontinuation (>30-day gap between prescription refills after expiration of the last prescription's supply),

switch to the study comparator, end of continuous enrollment in the health plan, or end of the study period (ie, December 31, 2018).

2.4 | Adjustment for confounders

To adjust for differences in baseline characteristics and disease risk factors, one SAC/VAL user was matched with up to 3 ARA users based on propensity score (PS) matched (1 up to 3) using the nearest neighbor method (0.05 caliper). Logistic regression was used to estimate the probability of initiating SAC/VAL or an ARA, conditional on baseline covariates during the year prior to the index date. The covariates considered were demographic variables (age, sex, type of benefit plan, and region of residence), and medical conditions reported in the literature as being associated with HF-related hospitalization (diabetes, hypertension, cerebrovascular disease, chronic obstructive pulmonary disease, dyslipidemia, coronary artery disease [CAD], chronic kidney disease [CKD] stages 3–5, anemia, peripheral vascular disease, heart valve disease, myocardial infarction [MI], depression, arrhythmias, hypotension and hypokalemia), oxygen use, and medications (ARB, ACEI, β-blocker, and loop diuretic). Medical conditions were captured by identifying patients with at least one relevant inpatient *ICD-9-CM* or *ICD-10-CM* code (complete code list can be found in Appendix S1). Medication use was measured using national drug codes between the first HFrEF hospital discharge and the index date on which SAC/VAL or an ARA was started. Time to initiation of SAC/VAL or ARA (from hospital discharge) measured in weeks, as well as total follow-up days, number of prior HF events, and all-cause healthcare setting visits prior to and including the index date were also used to calculate the PS. In addition to matching on PS, patients were exact matched on sex.

2.5 | Statistical analysis

Differences in baseline characteristics between SAC/VAL and ARA initiators were assessed with standardized differences (<0.1 absolute value considered well balanced). Rates of HF-related and all-cause readmissions were calculated as the number of events per 100 person-years and compared using multivariable Cox proportional hazards models. After 1 up to 3 PS matching, we also adjusted for the aforementioned covariates in the regression models, except for region of residence, type of benefit plan, and number of follow-up days. To account for clustering within matched sets, we used robust variance estimates. The proportionality assumption was assessed by review of Schoenfeld residuals and was found to be valid. We calculated and reported the *E*-value[18,19] to indicate the minimum strength of association that an unmeasured confounding factor would need to have with the treatment and outcome to explain away an association between treatment and hospitalizations.

We conducted several subgroup analyses, including age categories, sex, and selected comorbidities (diabetes, hypertension, CAD, CKD, MI, prior use of ACEI/ARB, and prior HF inpatient visit between first HFrEF discharge and index date). We also performed analyses on subgroups of patients using ACEI/ARB plus ARA and those who initiated treatment at least 6 weeks after hospital discharge. Patients were rematched within each subgroup for the analyses. Subgroup analyses, conducted in each subgroup, were equated to separate analyses and tested for interaction terms in a single regression model that included both groups. The P-value of the interaction term was reported ($p_{\text{interaction}}$). A $p_{\text{interaction}}$ value <0.05 was considered statistically significant. Sensitivity analyses were performed to examine the potential heterogeneity of treatment effects in time to initiation of SAC/VAL or ARA from first hospital discharge (6, 12, 18, and 24 weeks). All analyses were conducted using SAS, version 9.4 (SAS Institute Inc.; Cary, North Carolina).

3 | RESULTS

3.1 | Patient characteristics

We identified 1150 new SAC/VAL users and 10,008 new ARA users (Figure 1). After PS matching, 3927 patients were included in the cohort (1088 SAC/VAL users and 2839 ARA users). In the PS-matched cohort, patient demographic characteristics, comorbidities, healthcare utilization, and medication use were well balanced between the two treatment groups (all standardized differences <0.1) (Table 1).

3.2 | Outcomes

The mean and standard deviation (SD) follow-up times of matched SAC/VAL and ARA groups were 335 (262) days and 341 (285) days, respectively (Table 1). We identified 98 HF-related hospitalizations in the SAC/VAL group and 317 HF-related hospitalizations in the ARA group (Table 2). The crude HF-related hospitalization rate was 13 per 100 person-years for SAC/VAL users versus 18 per 100 person-years for ARA users. Risk of HF-related hospitalization was 27% lower among SAC/VAL users compared with ARA users (adjusted HR [aHR], 0.73; 95% confidence interval [CI], 0.58–0.91; $p = 0.006$). Descriptions of HF-related hospitalization events can be found in Table S1. We calculated the *E*-value to account for the impact of unobserved confounding factors on estimated HR for hospitalization. An unmeasured confounder would need to have a minimum risk ratio of 2.08, above and beyond measured confounders, to fully explain away the association between treatment and HF-related hospitalization (Table 2).

Among SAC/VAL users, there were 294 all-cause hospitalizations, or 42 per 100 person-years, compared with 954 all-cause hospitalizations, or 61 per 100 person-years, among ARA users. SAC/VAL users had a 31% lower risk of all-cause hospitalization (aHR, 0.69; 95% CI, 0.61–0.79; $p < 0.001$) compared with ARA users (Table 2). Descriptions of all-cause events can be found in Table S2. The *E*-value for the aHR estimate of all-cause hospitalization was 1.91 and for CI was 1.63 (Table 2). In other words, an unmeasured

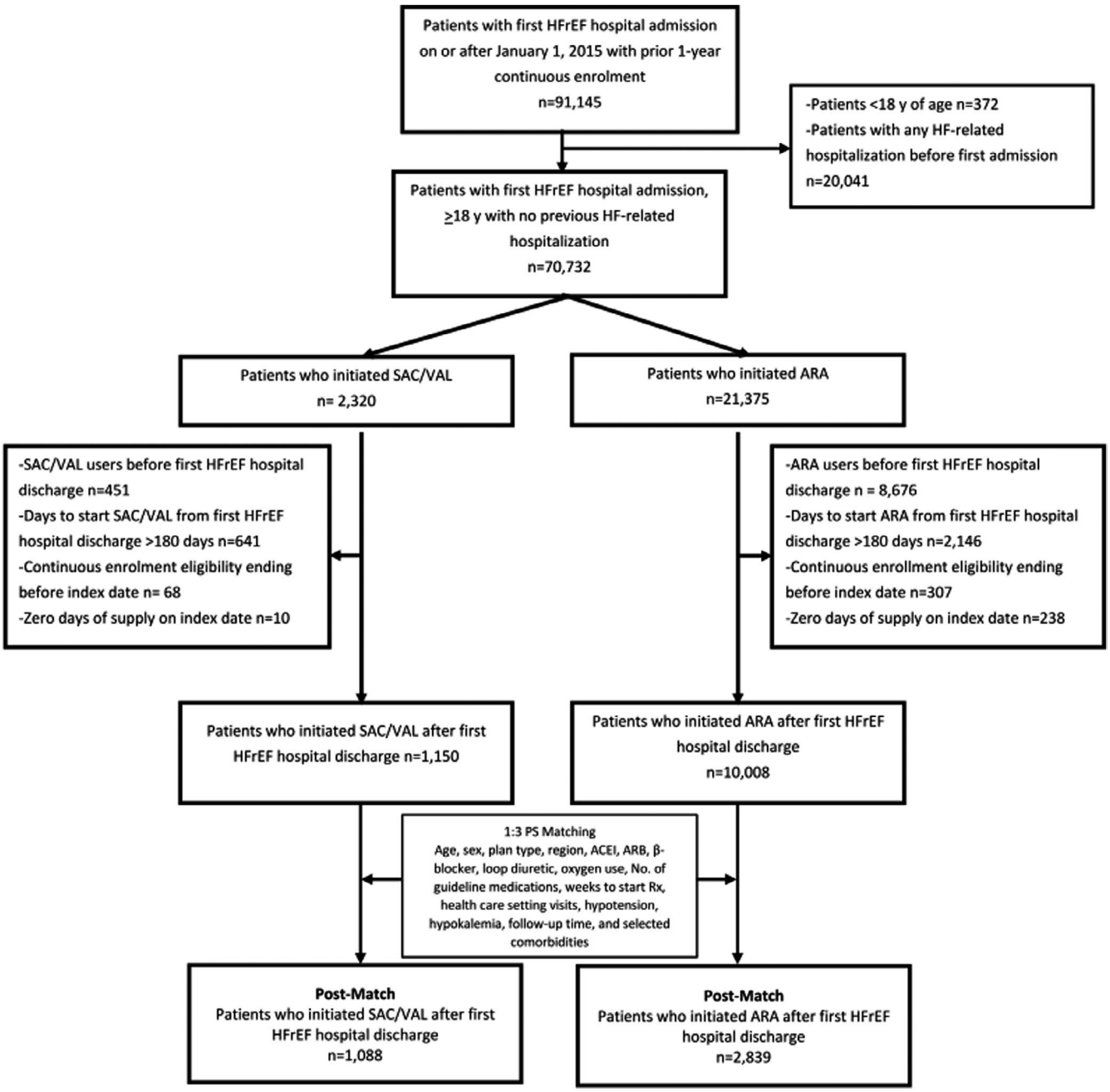

FIGURE 1 Study cohort flow diagram. ACEI, angiotensin-converting enzyme inhibitor; ARA, aldosterone antagonist; ARB, angiotensin receptor blocker; HFrEF, heart failure with reduced ejection fraction; PS, propensity score; Rx, prescription; SAC/VAL, sacubitril/valsartan

confounder would need to have a minimum risk ratio of 1.91, above and beyond measured confounders, to fully explain away the association between treatment and all-cause hospitalization (Table 2).

3.3 | Subgroup and sensitivity analyses

No statistically significant differences were observed across prespecified subgroup analyses for risk of HF-related hospitalization (Table 3) or all-cause hospitalization (Table 4). Similar results were observed in subgroups of SAC/VAL vs. ARA plus ACEI/ARB users (Table S3) and patients who initiated the treatment at least 6 weeks after hospital discharge (Table S4).

Study results remained unchanged in sensitivity analyses, including restriction to patients who started study medications within 6, 12, 18, or 24 weeks after the first HFrEF hospital discharge date (Table S5).

4 | DISCUSSION

To the best of our knowledge, this study reports the first real-world evaluation of the comparative effectiveness of SAC/VAL and ARAs,

TABLE 1 Demographics and clinical characteristics of patients with heart failure with reduced ejection fraction

	Unmatched			Matched		
Characteristics	**SAC/VAL users *n* = 1150**	**ARA users *n* = 10,008**	**Std diff**	**SAC/VAL users *n* = 1088**	**ARA users *n* = 2839**	**Std diff**
Age, mean (SD), years	61.3 (13.5)	62.9 (15.1)	−0.11	61.5 (13.5)	62.2 (15.3)	−0.05
Women, *n* (%)	344 (29.9)	3545 (35.4)	−0.12	324 (29.8)	886 (31.2)	−0.03
Type of benefit plan, *n* (%)						
Comprehensive	173 (15.0)	2204 (22.0)	−0.18	172 (15.8)	475 (16.7)	−0.03
EPO	5 (0.4)	78 (0.8)	−0.04	5 (0.5)	13 (0.5)	0.00
HMO	83 (7.2)	936 (9.4)	−0.08	83 (7.6)	208 (7.3)	0.01
POS	55 (4.8)	540 (5.4)	−0.03	55 (5.1)	154 (5.4)	−0.02
PPO	610 (53.0)	4648 (46.4)	0.13	580 (53.3)	1,514 (53.3)	0.00
POS with capitation	29 (2.5)	112 (1.1)	0.11	26 (2.4)	58 (2.0)	0.02
CDHP	100 (8.7)	826 (8.3)	0.02	97 (8.9)	242 (8.5)	0.01
HDHP	73 (6.4)	483 (4.8)	0.07	70 (6.4)	175 (6.2)	0.01
Region, *n* (%)						
Northeast	248 (21.6)	1906 (19.0)	0.06	233 (21.4)	616 (21.7)	−0.01
Northcentral	214 (18.6)	2740 (27.4)	−0.21	206 (18.9)	548 (19.3)	−0.01
South	615 (53.5)	4159 (41.6)	0.24	578 (53.1)	1495 (52.7)	0.01
West	73 (6.4)	1187 (11.9)	−0.19	71 (6.5)	180 (6.3)	0.01
Pre-index comorbidities, *n* (%)						
Anemia	143 (12.4)	1477 (14.8)	−0.07	137 (12.6)	352 (12.4)	0.01
Arrhythmia	542 (47.1)	4929 (49.3)	−0.04	517 (47.5)	1332 (46.9)	0.01
Cerebrovascular disease	147 (12.8)	1109 (11.1)	0.05	136 (12.5)	355 (12.5)	0.00
Chronic kidney disease	289 (25.1)	2161 (21.6)	0.96	273 (25.1)	735 (25.9)	0.01
Chronic obstructive pulmonary disease	161 (14.0)	1956 (19.5)	−0.15	134 (13.5)	375 (14.9)	−0.02
Coronary artery disease	568 (49.4)	4689 (46.9)	0.05	532 (48.9)	1427 (50.3)	−0.03
Diabetes	392 (34.1)	3142 (31.4)	0.06	361 (33.5)	956 (33.7)	−0.00
Depression	71 (6.2)	588 (5.9)	0.01	64 (5.9)	167 (5.9)	0.00
Dyslipidemia	451 (39.2)	3347 (33.4)	0.12	423 (38.9)	1069 (37.7)	0.03
Heart valve disorder	314 (27.3)	2991 (29.9)	−0.06	298 (27.4)	788 (27.8)	−0.01
Myocardial infarction	242 (21.0)	2430 (24.3)	−0.08	224 (20.6)	606 (21.4)	−0.02
Hypertension	558 (50.5)	5475 (54.7)	−0.08	549 (50.5)	1459 (51.4)	−0.02
Hypokalemia	120 (10.4)	1154 (11.5)	−0.04	116 (10.7)	314 (11.1)	−0.01
Hypotension	90 (7.8)	712 (7.1)	0.41	84 (7.7)	206 (7.3)	0.02
Peripheral vascular disease	55 (4.8)	667 (6.7)	−0.07	54 (5.0)	155 (5.5)	−0.02
Week to start Rx from index discharge, mean (SD)	8.0 (6.8)	4.0 (5.6)	0.63	7.7 (6.6)	6.6 (7.3)	0.16
Follow-up, mean (SD), days	329 (260)	485 (363)	−0.50	335 (262)	341 (285)	−0.02
Pre-index health facility visits, mean (SD)						
All-cause						
Inpatient visits	1.6 (1.0)	1.5 (1.0)	0.12	1.6 (1.0)	1.6 (1.0)	0.00
Outpatient visits	52.8 (50.2)	39.3 (44.2)	0.29	51.8 (49.8)	48.3 (49.5)	0.07
HF						
Inpatient visits[a]	0.1 (0.2)	0.1 (0.3)	−0.09	0.05 (0.2)	0.05 (0.2)	−0.02
Outpatient visits	2.7 (5.4)	1.8 (4.5)	0.19	2.7 (5.4)	2.5 (6.1)	0.04
Oxygen use, *n* (%)	12 (1.0)	115 (1.2)	−0.01	12 (1.1)	28 (1.0)	0.01

(Continues)

TABLE 1 (Continued)

Characteristics	Unmatched			Matched		
	SAC/VAL users *n* = 1150	ARA users *n* = 10,008	Std diff	SAC/VAL users *n* = 1088	ARA users *n* = 2839	Std diff
Recommended guideline medications, *n* (%)						
No., mean (SD)[b]	1.4 (0.8)	1.6 (0.8)	−0.23	1.4 (0.8)	1.4 (0.8)	0.05
ACEI	298 (25.9)	4899 (49.0)	−0.49	299 (26.8)	735 (25.9)	0.02
ARB	168 (14.6)	1473 (14.7)	−0.00	161 (14.8)	413 (14.6)	0.01
β-Blocker	973 (84.6)	7854 (78.5)	0.16	918 (84.4)	2309 (81.3)	0.08
Loop diuretic	798 (69.4)	7111 (71.1)	−0.04	763 (70.1)	1973 (69.7)	0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARA, aldosterone antagonist; ARB, angiotensin receptor blocker; CDHP, consumer directed health plan; EPO, exclusive provider organization; HDHP, high deductible health plan; HF, heart failure; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; Rx, prescription; SAC/VAL, sacubitril/valsartan; SD, standard deviation; Std diff, standardized difference.

[a]Inpatient visits were determined between first HFrEF hospital discharge and index date (patients had no HF inpatient visit before first HFrEF hospital admission).

[b]Number of recommended guideline medications includes ACEI/ARB, β-blocker, isosorbide dinitrate plus hydralazine, digoxin, and ivabradine used between index hospital discharge date and index prescription date.

TABLE 2 Risk of HF-related and all-cause hospitalizations with sacubitril/valsartan vs. aldosterone antagonists in propensity score-matched analyses

	Patients, *n*	Person-years	Events, *n*	Crude incidence per 100 person-years	Adjusted hazard ratio (95% CI)[a]	*p*-Value	*E*-value[b]
HF-related hospitalization							
Sacubitril/valsartan	1088	784	98	13	0.73 (0.58–0.91)	0.006	Estimate = 2.08 CI = 1.43
Aldosterone antagonist	2839	1793	317	18	Reference		
All-cause hospitalization							
Sacubitril/valsartan	1088	697	294	42	0.69 (0.61–0.79)	<0.001	Estimate = 1.91 CI = 1.63
Aldosterone antagonist	2839	1554	954	61	Reference		

Abbreviations: CI, confidence interval; HF, heart failure.

[a]Models were adjusted for age, sex, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, β-blocker, loop diuretics, oxygen use, No. of guideline medications used, healthcare setting visits (all-cause, HF-related), follow-up days, weeks from index hospital discharge to index prescription, anemia, coronary artery disease, cerebrovascular disease, peripheral vascular disease, diastolic heart failure, dyslipidemia, chronic kidney disease, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, depression, myocardial infarction, heart valve disease, arrhythmia, hypokalemia, and hypotension.

[b]*E*-value was calculated and interpreted to describe minimum strength of association of an unmeasured confounder with treatment and outcome.

both recommended therapies for HFrEF, in preventing the risk of HF-related or all-cause readmissions. In this retrospective cohort study of nearly 4000 PS-matched patients with HFrEF, we found that compared with using an ARA, using SAC/VAL was associated with significantly lower risk of HF-related readmission and all-cause hospitalization (Figure 2). Our subgroup analyses, which included baseline CKD, CAD, diabetes, and prior use of an ACEI or ARB, provided no evidence that the reduction in hospitalizations associated with SAC/VAL use varied among the evaluated patient subpopulations, even among those at increased risk of hospitalization.

In the PARADIGM-HF and PIONEER-HF trials, SAC/VAL decreased HF-related morbidity and cardiovascular mortality compared with enalapril among those who were using ACEI, beta-blocker, and/or ARAs.[5,20] Two observational studies using administrative claims databases evaluated the effectiveness of SAC/VAL compared with ARB/ACEI and found superior effects of SAC/VAL in reducing morbidity and mortality.[15,21] Another study indirectly compared SAC/VAL and ARA using data for primary endpoint from PARADIGM-HF and suggested beneficial effect of SAC/VAL over enalapril plus ARA.[22] More recently, the TRANSITION trial suggested that the use of SAC/VAL could be initiated early prior to or shortly after HF discharge.[23] Consequently, the 2021 update of the ACC expert consensus decision pathway of HF treatment recommends initiation of SAC/VAL or ACEI/ARB as a first-line therapy, though SAC/VAL is the preferred agent.[12]

We believe our study is a valuable addition to existing literature for clinicians who have patients already on ACEI/ARB plus β-blocker and are weighing the decision to initiate or switch to SAC/VAL or

TABLE 3 Risk of heart failure-related hospitalization with sacubitril/valsartan vs. aldosterone antagonists in propensity score-matched subgroup analyses

	Patients, *n*	Person-years	Events, *n*	Crude incidence per 100 person-years	Adjusted hazard ratio (95% CI)	$p_{Interaction}$
Age category, years						
18–44						0.62
Sacubitril/valsartan	96	62	6	10	0.52 (0.19–1.41)	
Aldosterone antagonist	223	153	23	15	Reference	
45–64						
Sacubitril/valsartan	582	421	41	10	0.73 (0.51–1.04)	
Aldosterone antagonist	1417	919	131	14	Reference	
≥65						
Sacubitril/valsartan	366	275	49	18	0.76 (0.55–1.05)	
Aldosterone antagonist	989	657	151	23	Reference	
Sex						
Men						0.52
Sacubitril/valsartan	758	555	64	12	0.65 (0.49–0.86)	
Aldosterone antagonist	1943	1202	209	17	Reference	
Women						
Sacubitril/valsartan	323	220	34	15	0.90 (0.60–1.37)	
Aldosterone antagonist	886	572	99	17	Reference	
Prior ACEI/ARB[a]						
Present						0.28
Sacubitril/valsartan	440	318	35	11	0.64 (0.44–0.94)	
Aldosterone antagonist	1169	725	127	18	Reference	
Absent						
Sacubitril/valsartan	622	452	63	14	0.81 (0.60–1.08)	
Aldosterone antagonist	1604	1062	183	17	Reference	
Diabetes						
Present						0.88
Sacubitril/valsartan	345	257	40	16	0.72 (0.50–1.05)	
Aldosterone antagonist	823	522	111	21	Reference	
Absent						
Sacubitril/valsartan	723	514	59	11	0.76 (0.57–1.00)	
Aldosterone antagonist	1854	1159	182	16	Reference	
Hypertension						
Present						0.86
Sacubitril/valsartan	543	416	59	14	0.81 (0.59–1.10)	
Aldosterone antagonist	1449	963	169	18	Reference	
Absent						
Sacubitril/valsartan	528	355	40	11	0.65 (0.46–0.92)	
Aldosterone antagonist	1334	857	138	16	Reference	
Chronic kidney disease						
Present						0.11
Sacubitril/valsartan	258	170	22	13	0.42 (0.26–0.70)	
Aldosterone antagonist	666	349	104	30	Reference	
Absent						
Sacubitril/valsartan	803	602	69	11	0.79 (0.60–1.04)	
Aldosterone antagonist	2075	1444	208	14	Reference	

(Continues)

TABLE 3 (Continued)

	Patients, *n*	Person-years	Events, *n*	Crude incidence per 100 person-years	Adjusted hazard ratio (95% CI)	$p_{Interaction}$
Coronary artery disease						
Present						0.39
Sacubitril/valsartan	521	372	55	15	0.83 (0.60–1.15)	
Aldosterone antagonist	1355	859	149	17	Reference	
Absent						
Sacubitril/valsartan	542	389	41	11	0.60 (0.50–0.73)	
Aldosterone antagonist	1409	883	146	17	Reference	
Prior inpatient visit for heart failure[a]						
Yes						0.27
Sacubitril/valsartan	43	30	5	17	0.22 (0.07–0.71)	
Aldosterone antagonist	105	60	28	47	Reference	
No						
Sacubitril/valsartan	1043	748	94	13	0.75 (0.59–0.96)	
Aldosterone antagonist	2674	1687	273	16	Reference	
Myocardial infarction						
Present						0.21
Sacubitril/valsartan	209	154	23	15	1.06 (0.61–1.83)	
Aldosterone antagonist	539	361	48	13	Reference	
Absent						
Sacubitril/valsartan	856	611	75	12	0.70 (0.54–0.90)	
Aldosterone antagonist	2258	1416	250	18	Reference	

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval.
[a]Between first heart failure with reduced ejection fraction hospital discharge date and index date.

the addition of ARAs with considerations to dosing, cost, and/or hemodynamic instability at baseline, or in patients where it is not likely both agents could be tolerated if co-administered. Although Escobar et al reported that using SAC/VAL was potentially associated with decreased risk of cardiovascular death compared with the use of enalapril with ARAs, the findings are limited due to differences in baseline clinical profile between the two groups, indirect comparisons from clinical trial data, which was designed for comparisons of SAC/VAL and enalapril regardless the use of ARAs.[22] Our study compared the two groups directly after PS matching which included their baseline clinical characteristics, healthcare utilization, and use of ACEI, ARB, B-blockers, and diuretics.

ARAs can be added to HF therapy for patients whose creatinine clearance is >30 ml/min and potassium <5.0 mEq/L. As a combination agent, SAC/VAL inhibits the renin-angiotensin-aldosterone system (RAAS) as well as neprilysin, leading to an elevation in the level of beneficial proteins in the natriuretic peptide (NP) system [ie, arterial (ANP), B-type (BNP), and C-type (CNP)]. Those proteins lead to induction of diuresis and natriuresis, inhibition of RAAS and the sympathetic nervous system, and to antifibrotic, antithrombotic, and antiproliferative effects.[24] ARAs are added to ACEIARB and β-blockers[11] to antagonize the effects of activated neurohormonal systems, such as RAAS.[25] The combination of systems inhibited by SAC/VAL provides greater clinical benefit than inhibition of only one system and may explain the greater reduction in hospitalization observed for the SAC/VAL users in our study.

There are several clinical implications of the results reported here. Our findings provide evidence to support current guidance[12,22] that SAC/VAL is a preferred agent for reducing risk of HF-related and all-cause hospitalizations in patients with HFrEF regardless of prior use of ACEI/ARB, and with or without CAD or CKD. Thus, this study provides evidence for making decisions regarding next step therapy for patients already on ACEI/ARB. Although our findings suggested that SAC/VAL was more effective than ARAs for treatment of patients with HFrEF to prevent HF-related and all-cause readmissions, other factors (eg, drug costs,[26] renal function, baseline blood pressure, regular monitoring, history of angioedema, and adverse events) also need to be considered. In addition, our findings do not preclude the potential value of using SAC/VAL and ARA together, SAC/VAL and an SGLT2 inhibitor, or SAC/VAL in combination with ARA and SGLT2 as suggested by recent update,[12] although there could be certain patients who are only able to take one of these agents for a variety of reasons such as cost, blood glucose, blood pressure, and serum potassium.

Our study has several important strengths. First, we incorporated subgroup analyses, including MI, CKD, and CAD, that were not reported in the PARADIGM-HF trial. Second, this study used PS matching to control for imbalances between treatment groups, a study design that included only new users of the study drugs, and

TABLE 4 Risk of all-cause hospitalization with sacubitril/valsartan vs. aldosterone antagonists in propensity score-matched subgroup analyses

	Patients, *n*	Person-years	Events, *n*	Crude incidence per 100 person-years	Adjusted hazard ratio (95% CI)	$p_{Interaction}$
Age category, years						
18–44						0.09
Sacubitril/valsartan	96	61	19	31	0.66 (0.36–1.20)	
Aldosterone antagonist	223	137	54	39	Reference	
45–64						
Sacubitril/valsartan	582	381	122	32	0.61 (0.50–0.75)	
Aldosterone antagonist	1417	806	429	53	Reference	
≥65						
Sacubitril/valsartan	366	233	149	64	0.79 (0.66–0.96)	
Aldosterone antagonist	989	557	433	78	Reference	
Sex						
Men						0.54
Sacubitril/valsartan	758	490	206	42	0.68 (0.58–0.79)	
Aldosterone antagonist	1943	1042	657	63	Reference	
Women						
Sacubitril/valsartan	323	202	87	43	0.66 (0.51–0.86)	
Aldosterone antagonist	886	481	302	63	Reference	
Prior ACEI/ARB[a]						
Present						0.95
Sacubitril/valsartan	440	282	112	40	0.68 (0.55–0.84)	
Aldosterone antagonist	1169	632	388	61	Reference	
Absent						
Sacubitril/valsartan	622	404	180	45	0.71 (0.60–0.84)	
Aldosterone antagonist	1604	922	551	60	Reference	
Diabetes						
Present						0.30
Sacubitril/valsartan	345	217	118	54	0.77 (0.62–0.95)	
Aldosterone antagonist	823	439	307	70	Reference	
Absent						
Sacubitril/valsartan	723	471	173	37	0.66 (0.56–0.79)	
Aldosterone antagonist	1854	1017	568	56	Reference	
Hypertension						
Present						0.17
Sacubitril/valsartan	543	363	166	46	0.78 (0.65–0.93)	
Aldosterone antagonist	1449	853	482	56	Reference	
Absent						
Sacubitril/valsartan	528	322	128	40	0.64 (0.53–0.78)	
Aldosterone antagonist	1334	668	425	64	Reference	
Chronic kidney disease						
Present						0.28
Sacubitril/valsartan	258	153	74	49	0.59 (0.46–0.76)	
Aldosterone antagonist	666	318	250	79	Reference	
Absent						
Sacubitril/valsartan	803	536	209	39	0.70 (0.60–0.81)	
Aldosterone antagonist	2075	1245	695	56	Reference	

(Continues)

TABLE 4 (Continued)

	Patients, *n*	Person-years	Events, *n*	Crude incidence per 100 person-years	Adjusted hazard ratio (95% CI)	$p_{Interaction}$
Coronary artery disease						
Present						0.07
Sacubitril/valsartan	521	319	167	52	0.81 (0.67–0.96)	
Aldosterone antagonist	1355	759	476	63	Reference	
Absent						
Sacubitril/valsartan	542	362	119	33	0.60 (0.50–0.73)	
Aldosterone antagonist	1409	781	434	56	Reference	
Prior inpatient visit for heart failure[a]						
Yes						0.86
Sacubitril/valsartan	43	23	16	69	0.53 (0.22–1.27)	
Aldosterone antagonist	105	54	48	88	Reference	
No						
Sacubitril/valsartan	1043	673	276	41	0.66 (0.58–0.75)	
Aldosterone antagonist	2674	1473	898	61	Reference	
Myocardial infarction						
Present						0.19
Sacubitril/valsartan	209	134	65	48	0.78 (0.60–1.01)	
Aldosterone antagonist	539	303	187	62	Reference	
Absent						
Sacubitril/valsartan	856	547	224	41	0.65 (0.56–0.75)	
Aldosterone antagonist	2258	1233	773	63	Reference	

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval.

[a]Between first heart failure with reduced ejection fraction hospital discharge date and index date.

Cox proportional hazards models for analysis of matched groups, a doubly robust analysis, which is a relatively robust method for estimating treatment effects compared with matching or regression alone. Third, we included only patients who had an initial hospital admission with HFrEF and no HF-related hospitalization in the prior year as a proxy to minimize confounding by disease severity. We reported E-value to provide evidence of robustness of our findings to potential unmeasured confounding. Fourth, this study used a large commercial database representative of the US population covered under employer-based medical insurance. Finally, the large sample size allowed us to conduct several subgroup and sensitivity analyses to assess the robustness of the results.

Nevertheless, this study also has some limitations. We did not have information on echocardiogram or ejection fraction test results or laboratory results (eg, B-type natriuretic peptide, N-terminal pro-B-type natriuretic peptide, or cardiac enzyme levels) to corroborate ICD codes for HFrEF diagnosis, and residual confounding may exist because of this missing information. However, we reported E-value results to show that our findings were less likely to be affected by unmeasured confounders. We attempted to minimize the misclassification bias risk by using validated ICD code algorithms for HFrEF identification. This study also lacked information on race and ethnicity, precluding analyses of these subgroups. The pathophysiology of HF may vary among racial/ethnic groups, potentially explaining why some treatments may be superior to others.[14] Because we used an administrative claims database for prescription fills, we could not be sure that patients actually consumed the prescribed medications. But the proportion of patients who refilled their prescription was high, suggesting that patients had consumed the medication. Although we observed associations with HF-related and all-cause hospitalizations, it was not possible to assess mortality, an important outcome in HF, because comprehensive death information was not available in our dataset. Further study is required to determine whether the observed results for hospitalizations hold true for mortality. The patients included in this study had private and Medicare Advantage plans; thus, our findings may not be generalizable to patients with other health insurance plans or to patients without insurance. Patients included in the study had no HF hospitalizations in the year prior to entry in the cohort, which may represent a comparatively stable population. To mitigate this weakness, we provided a subgroup analysis of patients who had multiple hospitalizations between first HFrEF admission and therapy initiation. Although we could not completely avoid the impact of confounding by indication or severity because prescribing practices may have varied, we used PS matching to reduce confounding. However, PS matching helps control for only observed variables; bias related to latent or unmeasured variables may persist even after matching. Additionally, E-value was reported to show that unmeasured confounders did not have such association with the outcome to move the estimated effects in any other direction. A limitation of generalizability

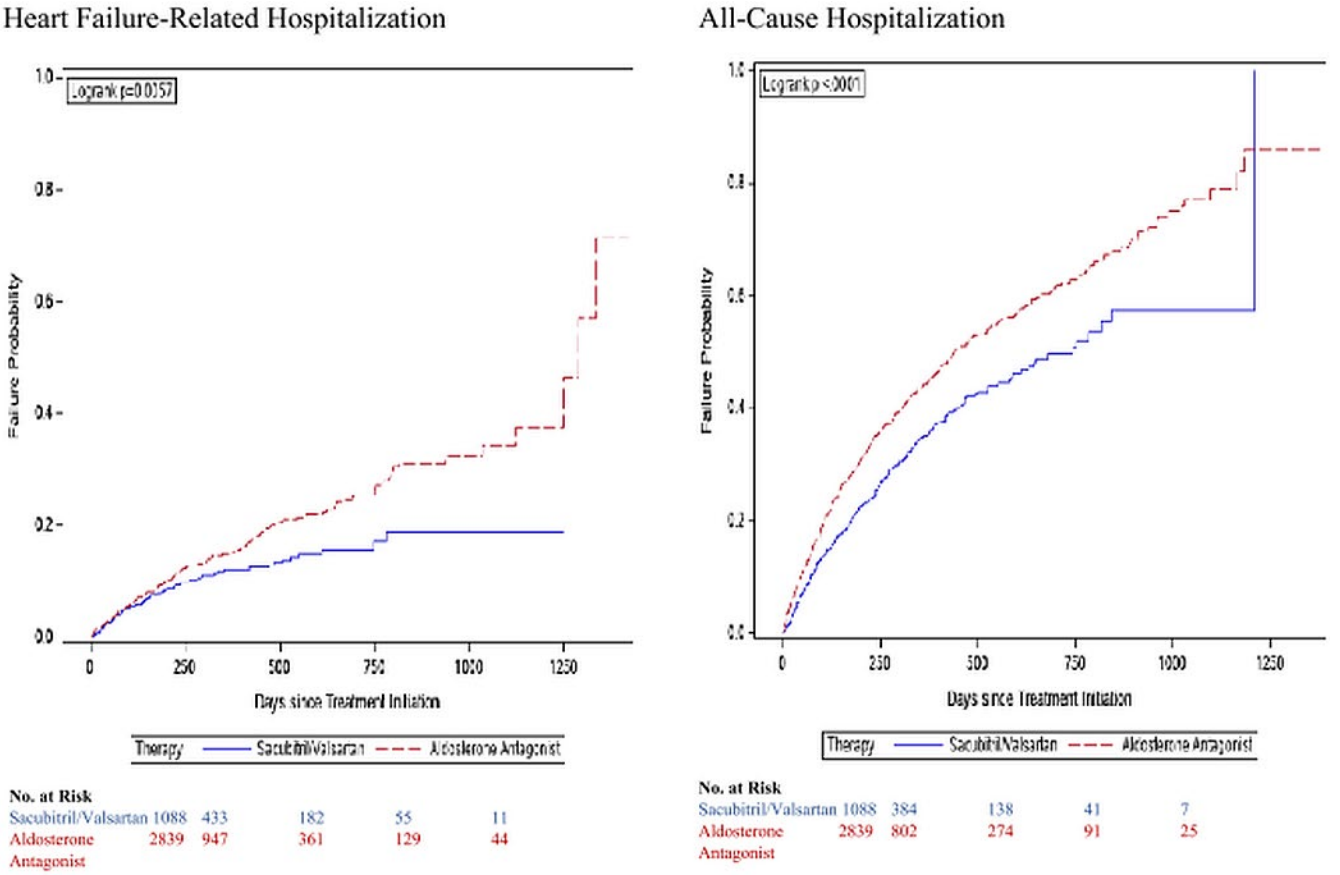

FIGURE 2 Risk of outcomes in patients treated with sacubitril/valsartan or aldosterone antagonist for heart failure with reduced ejection fraction

in the ARA group could have been introduced by exclusion of large number of patients in the ARA group as they were not matched with patients in the SAC/VAL group.

5 | CONCLUSIONS

Our study findings indicated that in patients with HFrEF, compared with ARA therapy, treatment with SAC/VAL was associated with decreased HF-related hospitalization and all-cause hospitalization. The decreased hospitalization with SAC/VAL use extended to selected subgroups that were evaluated in the present study but that were not assessed in the original clinical trial, including patients with CKD or CAD. To reduce pill burden and improve clinical outcomes, switching to SAC/VAL before adding ARA can be a viable option for patients, already on ACEI/ARBs, having commercial insurance coverage.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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