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ORIGINAL RESEARCH

Hospitalization Rates in Patients with Heart Failure and Reduced Ejection Fraction Initiating Sacubitril/Valsartan or Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers: A Retrospective Cohort Study

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ABSTRACT

Introduction: The angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan (SAC/VAL) has shown benefit in patients with symptomatic heart failure (HF), including those naïve to renin–angiotensin–aldosterone system inhibitor (RAASi) therapy, and is considered the preferred RAASi for chronic HF. Real-world data on ARNI, specifically in RAASi-naïve patients, are limited. This study compared real-world outcomes of ARNI (SAC/VAL) vs. angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) therapy in RAASi-naïve patients with HF and reduced ejection fraction (HFrEF).

Methods: This retrospective cohort study included de-identified data on RAASi-naïve patients with HFrEF (left ventricular ejection fraction $\leq$ 40%) who had newly initiated SAC/VAL or ACEi/ARB between July 1, 2015, and March 31, 2019, from the Optum® Electronic Health Records database in the US. New SAC/VAL users were propensity score matched 1:2 with new ACEi/ARB users by pre-selected characteristics. One-year post-index rates of all-cause, HF, and cardiovascular hospitalizations and the composite of HF hospitalization or emergency room (ER) visits were measured using negative binomial regression. Time to first all-cause hospitalization, HF hospitalization, and composite of HF hospitalization or ER visits was measured using a subdistribution hazards model.

Results: The matched sample included 3059 new SAC/VAL and 6118 new ACEi/ARB users. Rates of all-cause hospitalization and composite of HF hospitalization or ER visits were significantly lower with SAC/VAL compared with ACEi/ARB (incidence rate ratio [95% confidence interval]: 0.87 [0.81–0.93] and 0.87 [0.81–0.94], respectively), whereas rates of HF hospitalizations and cardiovascular hospitalizations were similar (1.00 [0.91–1.11] and 0.94 [0.87–1.02], respectively). Time-to-event analyses also showed a similar trend.

Conclusions: In real-world clinical practice, RAASi-naïve patients with HFrEF initiating SAC/VAL were less likely to be hospitalized than those initiating ACEi/ARB, suggesting a potential for a reduced clinical and economic burden

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in these patients.**Keywords:** Angiotensin-converting enzyme inhibitor; Angiotensin receptor blocker; Angiotensin receptor neprilysin inhibitor; Heart failure; Sacubitril/valsartan

Key Summary Points

Why carry out this study?

There is a scarcity of real-world outcomes data in patients with heart failure and reduced ejection fraction (HFrEF) initiating an angiotensin receptor neprilysin inhibitor (ARNI) who have not previously received a renin–angiotensin–aldosterone system inhibitor (RAASi).

This is the first study that specifically focuses on RAASi-naïve patients with HFrEF and demonstrated the benefit of an ARNI (sacubitril/valsartan [SAC/VAL]) compared with traditional first-line therapies (angiotensin-converting enzyme inhibitors [ACEi]/angiotensin receptor blockers [ARB]) in a real-world setting.

What was learned from the study?

The results of the present real-world study demonstrate the clinical benefit of directly initiating SAC/VAL rather than traditional first-line therapies, such as ACEi/ARB, in patients with HFrEF.

The benefit of sacubitril/valsartan (SAC/VAL) over ACEi/ARB in RAASi-naïve patients with HFrEF observed in this study validates the findings of a randomized controlled trial, PIONEER-HF, where SAC/VAL was found to be superior to enalapril in a subgroup of RAASi-naïve patients.

In patients with HFrEF naïve to RAAS inhibition, healthcare providers need to consider the benefit of initiating ARNI in reducing all-cause hospitalizations, thereby potentially reducing the overall disease burden.

INTRODUCTION

Heart failure (HF) affects approximately 6 million adults in the United States (US) [1], and its prevalence is projected to increase by 15% globally and by 23% in the US by 2030 [2]. The renin–angiotensin–aldosterone system (RAAS) inhibition is the cornerstone of therapy for HF with reduced ejection fraction (HFrEF; left ventricular ejection fraction [LVEF] $\leq$ 40%), which has traditionally included angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) [3, 4]. Sacubitril/valsartan (SAC/VAL) is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), which simultaneously delivers RAAS inhibition through valsartan and neprilysin inhibition through sacubitril. SAC/VAL was first approved by the US Food and Drug Administration in July 2015 for the treatment of chronic HFrEF [5]. The latest update of the American College of Cardiology (ACC) Expert Consensus Decision Pathway (ECDP) on HF treatment recommends ARNI as the preferred RAAS inhibitor (RAASi) for HFrEF in patients who have been previously treated with an ACEi or ARB, as well as in patients naïve to an ACEi or ARB [6]. SAC/VAL has shown superiority over enalapril in reducing all-cause mortality and HF hospitalization in patients with HFrEF and New York Heart Association (NYHA) class II-IV who had been previously treated with an ACEi/ARB in the PARADIGM-HF trial [7], and in patients hospitalized with acute decompensated HF in the PIONEER-HF trial [8–10]. Moreover, there is increasing evidence of the effectiveness and safety of SAC/VAL in real-world clinical practice [11–17]. Subgroup analyses of clinical trials, including PIONEER-HF [10] and PROVE-HF [18], have shown a consistent benefit of SAC/VAL in ACEi/ARB-naïve patients as in those with prior exposure. This is complemented by data showing consistent safety and tolerability in ACEi/ARB-naïve patients from PIONEER-HF [10] and TRANSITION-HF [19]. However, there are limited data on this patient population in the real-world setting. Because patients with HF who are naïve to RAAS inhibition may differ from those with prior exposure in terms of baseline

characteristics and tolerability to new treatments, it is of interest to evaluate the real-world effectiveness of SAC/VAL specifically in patients naïve to RAAS inhibition. Therefore, we aimed to compare the hospitalization rates and time to hospitalization between RAASi-naïve patients with HFrEF initiating SAC/VAL and those initiating traditional first-line ACEi/ARB therapy, using data from the US Optum® Electronic Health Records (EHR) database.

METHODS

Study Design and Data Sources

This retrospective cohort study was conducted using secondary data from a large US EHR database provided by OptumLabs spanning the period from July 1, 2014, to December 31, 2019 (Fig. 1). The Optum EHR database contains de-identified and aggregated clinical medical administrative data from 85 US healthcare delivery organizations spread across 50 states. Clinical and other medical administrative data available from the Optum database were obtained from both inpatient and ambulatory EHRs, practice management systems, and numerous other internal systems. Institutional review board approval was deemed unnecessary because the information retrieved from the database was de-identified.

Patient Identification and Cohort Assignment

The study included adult patients (≥ 18 years of age) with at least one International Classification of Diseases-9-Clinical Modification (ICD-9-CM) or ICD-10-CM code for a diagnosis of HF within 1 year prior to the index date. Eligible patients were required to have an LVEF of ≤ 40% at the latest assessment in the pre-index period and an initial prescription of SAC/VAL or ACEi/ARB during the identification period (i.e., between July 1, 2015, and March 31, 2019). The ICD-9-CM and ICD-10-CM codes used for the diagnosis of HF are provided in Table 1. SAC/VAL and ACEi/ARB could be prescribed in either inpatient or outpatient settings. Patients were required to be naïve (without prescription) to both SAC/VAL and ACEi/ARB treatments for 365 days before the index date. The index date was defined as the first date of prescription of SAC/VAL or ACEi/ARB during the identification period. Patients with a first-time SAC/VAL prescription and no ACEi/ARB prescription in the 365 days preceding the SAC/VAL index date were assigned to the SAC/VAL cohort (new SAC/VAL users), and patients with a first-time ACEi/ARB prescription and no ACEi/ARB prescription in the 365 days preceding the ACEi/ARB index date were assigned to the ACEi/ARB cohort (new ACEi/ARB users).

Because information on continuous enrollment in the health plan was not available from the database, a proxy measure was used to identify patients who had their first date being active in a plan was 365 days before the index

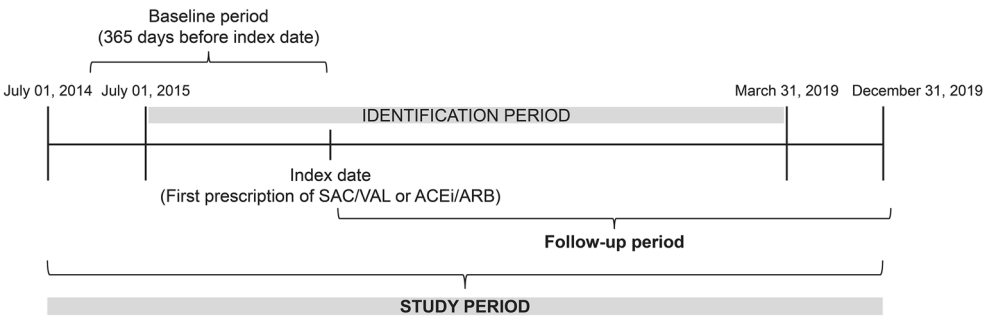

Fig. 1 Study design. *SAC/VAL* sacubitril/valsartan, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker

Table 1 ICD-9-CM and ICD-10-CM codes used for HF diagnosis

Disease	ICD-9-CM	ICD-10-CM
HF	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428, 428.0, 428.1, 428.2, 428.20, 428.21, 428.22, 428.23, 428.3, 428.30, 428.31, 428.32, 428.33, 428.4, 428.40, 428.41, 428.42, 428.43, 428.9	I09.81, I11.0, I13.0, I13.2, I50, I50.1, I50.2, I50.20, I50.21, I50.22, I50.23, I50.3, I50.30, I50.31, I50.32, I50.33, I50.4, I50.40, I50.41, I50.42, I50.43, I50.8, I50.81, I50.810, I50.811, I50.812, I50.813, I50.814, I50.82, I50.83, I50.84, I50.89, I50.9, I97.13, I97.130, I97.131
Cardiomyopathy	674.54, 674.53, 674.52, 674.51, 674.50, 674.5, 425.9, 425.8, 425.7, 425.5, 425.2, 425.18, 425.11, 425, 425.1	A36.81, B33.24, I25.5, I42, I42.0, I42.1, I42.2, I42.5, I42.6, I42.7, I42.9, I43, O90.3

HF heart failure, *ICD* International Classification of Diseases, *CM* Clinical Modification

date and last date being active in a plan was on or beyond the index date. Patients were followed until December 31, 2019 (end of study), death, or health plan disenrollment. Patients were also required to have no missing data for sex and year of birth. Furthermore, patients who had no valid SAC/VAL prescription on the index or 365 days before the index date and were subsequently prescribed SAC/VAL were excluded from the new ACEi/ARB cohort to keep the two cohorts mutually exclusive.

Outcomes

The primary endpoint assessed in the study was the rate of HF hospitalizations for both new SAC/VAL users and new ACEi/ARB users during the post-index period. Secondary endpoints included the rate of the composite of HF hospitalization or emergency room (ER) visits, rate of all-cause hospitalizations, rate of cardiovascular hospitalizations, time to first HF hospitalization, time to first HF hospitalization or ER visit, and time to first all-cause hospitalization for new SAC/VAL users and new ACEi/ARB users during the post-index period. HF hospitalizations and HF ER visits were defined per ICD-9-CM and ICD-10-CM codes for HF listed within the primary diagnoses associated with a hospitalization or an ER visit, respectively, that occurred during the follow-up period. All-cause hospitalizations were defined as any hospitalization that occurred during the follow-up period.

Statistical Methods

A feasibility analysis conducted in the Optum EHR database identified 1453 adults with HFrEF between July 1, 2015, and June 30, 2018, with at least 1 year of follow-up from the initial SAC/VAL prescription and naïve to SAC/VAL, ACEi, and ARB for at least 1 year prior to the index date. It was estimated that the study would be able to detect a response rate ratio of < 0.86 or > 1.16 using an anticipated event rate of 0.249 (lowest hospitalization rate reported), a sample size of 1400, a mean exposure time of 1 year, and an over-dispersion parameter of 1.0, to generate results with 0.8 (1-beta) power at a 0.05 (two-sided alpha) significance level.

The new SAC/VAL users and new ACEi/ARB users were propensity score matched 1:2 using a greedy many-to-one algorithm to account for potential bias and confounding. The patients were matched on selected demographics and pre-index baseline characteristics, including age; sex; year of index date; race; ethnicity; geographical region; Elixhauser Comorbidity Index (ECI); comorbidities; signs or symptoms; LVEF; background medications; and previous all-cause hospitalization, HF hospitalization, HF-specific outpatient visit, and HF-specific ER visit in the preceding year. Unmatched patients

Table 2 Demographic characteristics of patients before and after propensity score matching

Characteristics	Before propensity score matching				After propensity score matching			
	New SAC/VAL users (*N* = 3367)	New ACEi/ARB users (*N* = 50,872)	SMD (%)	*P* value	New SAC/VAL users (*N* = 3059)	New ACEi/ ARB users (*N* = 6118)	SMD (%)	*P* value
Age (years) at index, mean (SD)	65.92 (13.08)	66.94 (13.74)	7.64	< 0.0001	66.02 (13.08)	66.18 (14.01)	1.20	0.19
Sex, *n* (%)								
Female	967 (28.72)	17,927 (35.24)	14.01	< 0.0001	909 (29.72)	1829 (29.90)	0.39	0.86
Male	2400 (71.28)	32,945 (64.76)	14.01		2150 (70.28)	4289 (70.10)	0.39	
Year of index, *n* (%)								
2015	92 (2.73)	8505 (16.72)	48.57	< 0.0001	92 (3.01)	198 (3.24)	1.32	0.92
2016	638 (18.95)	18,140 (35.66)	38.18		636 (20.79)	1291 (21.10)	0.76	
2017	1040 (30.89)	12,688 (24.94)	13.29		991 (32.40)	1980 (32.36)	0.07	
2018	1239 (36.80)	9377 (18.43)	41.97		1056 (34.52)	2109 (34.47)	0.10	
2019	358 (10.63)	2162 (4.25)	24.50		284 (9.28)	540 (8.83)	1.59	
Race, *n* (%)								
African American	549 (16.31)	8409 (16.53)	0.61	0.01	498 (16.28)	1000 (16.35)	0.18	0.89
Asian	36 (1.07)	402 (0.79)	2.91		30 (0.98)	71 (1.16)	1.75	
Caucasian	2669 (79.27)	39,849 (78.33)	2.29		2422 (79.18)	4827 (78.90)	0.68	
Other/ unknown	113 (3.36)	2212 (4.35)	5.16		109 (3.56)	220 (3.60)	0.18	
Ethnicity, *n* (%)								
Hispanic	95 (2.82)	1810 (3.56)	4.19	0.03	86 (2.81)	173 (2.83)	0.10	0.99
Not Hispanic	3097 (91.98)	46,696 (91.79)	0.70		2822 (92.25)	5647 (92.30)	0.18	
Unknown	175 (5.20)	2366 (4.65)	2.53		151 (4.94)	298 (4.87)	0.30	
Geographical region, *n* (%)								
Midwest	1349 (40.07)	23,556 (46.30)	12.62	< 0.0001	1268 (41.45)	2543 (41.57)	0.23	0.98
Northeast	512 (15.21)	6533 (12.84)	6.81		474 (15.50)	943 (15.41)	0.23	
South	1326 (39.38)	15,447 (30.36)	19.01		1146 (37.46)	2290 (37.43)	0.07	
West	99 (2.94)	3917 (7.70)	21.33		96 (3.14)	202 (3.30)	0.93	
Other/ unknown	81 (2.41)	1419 (2.79)	2.41		75 (2.45)	140 (2.29)	1.07	

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *SAC/VAL* sacubitril/valsartan, *SD* standard deviation, *SMD* standardized mean difference

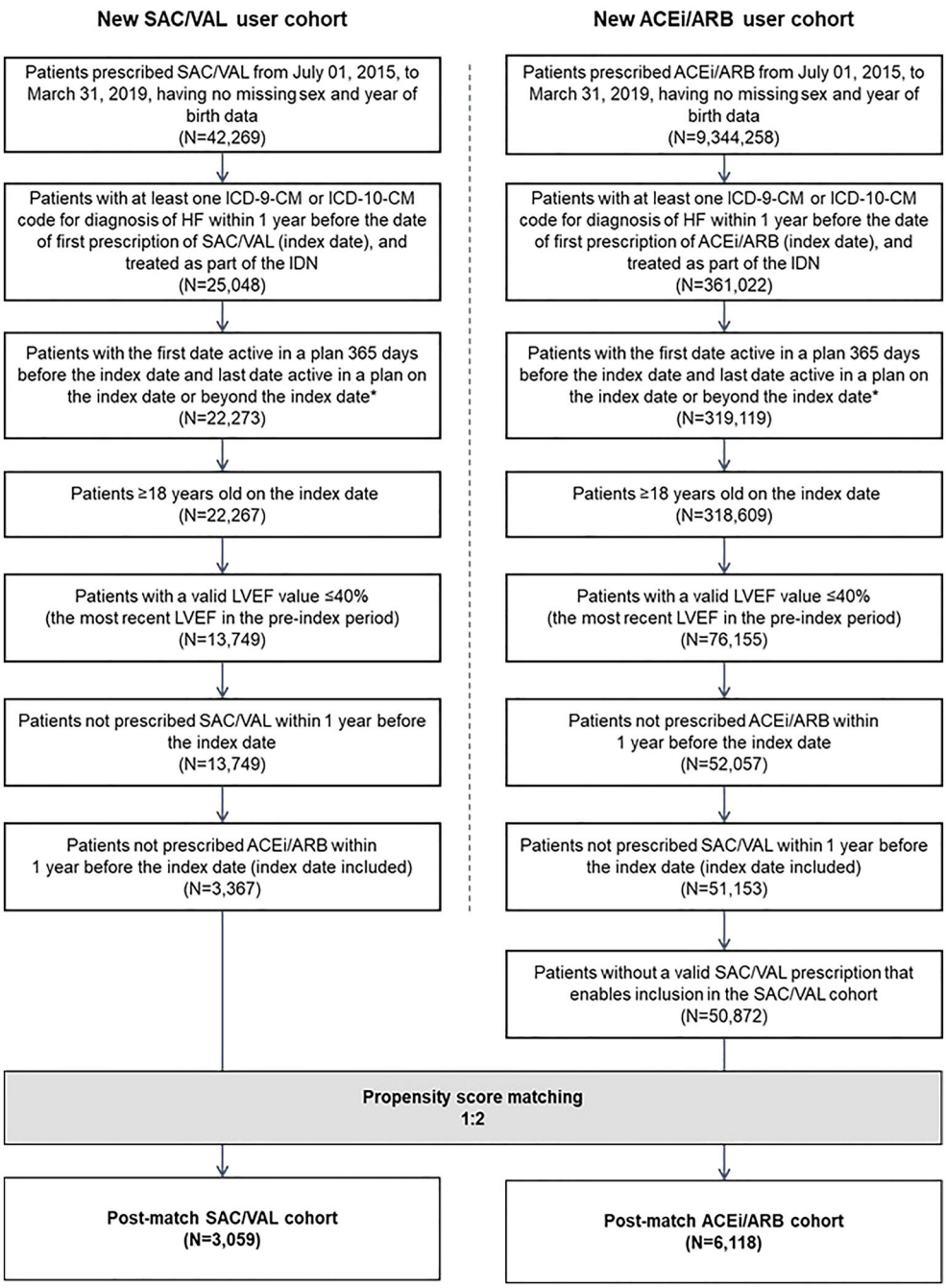

Fig. 2 Patient selection. *Criteria used as a proxy for the continuous enrollment in the Optum EHR database as this information was not directly available. *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CM* Clinical Modification, *EHR* electronic health record, *HF* heart failure, *ICD* International Classification of Diseases, *IDN* Integrated Delivery Network, *LVEF* left ventricular ejection fraction, *SAC/VAL* sacubitril/valsartan

Table 3 Distribution of comorbidities, signs, and symptoms before and after propensity score matching

Characteristics	Before propensity score matching				After propensity score matching			
	New SAC/VAL users (*N* = 3367)	New ACEi/ARB users (*N* = 50,872)	SMD (%)	*P* value	New SAC/VAL users (*N* = 3059)	New ACEi/ARB users (*N* = 6118)	SMD (%)	*P* value
ECI[a], *n* (%)								
Low ECI score < 0	9 (0.27)	205 (0.40)	2.35	–	9 (0.29)	33 (0.54)	3.81	–
Mild ECI score 0	7 (0.21)	220 (0.43)	3.98		5 (0.16)	41 (0.67)	7.87	
Moderate ECI score 1–4	87 (2.58)	1540 (3.03)	2.68		83 (2.71)	203 (3.32)	3.54	
Severe ECI score ≥ 5	3264 (96.94)	48,907 (96.14)	4.40		2962 (96.83)	5841 (95.47)	7.06	
Comorbidities, signs and symptoms, *n* (%)								
Altered consciousness	100 (2.97)	3699 (7.27)	19.61	< 0.0001	99 (3.24)	171 (2.80)	2.58	0.24
Anemia (including iron deficiency)	204 (6.06)	4319 (8.49)	9.37	< 0.0001	199 (6.51)	416 (6.80)	1.18	0.60
COPD	630 (18.71)	11,525 (22.65)	9.75	< 0.0001	594 (19.42)	1128 (18.44)	2.50	0.26
Dementia	66 (1.96)	3115 (6.12)	21.26	< 0.0001	65 (2.12)	124 (2.03)	0.69	0.76
Depression	342 (10.16)	6362 (12.51)	7.41	< 0.0001	322 (10.53)	588 (9.61)	3.04	0.17
Diabetes mellitus	1202 (35.70)	18,990 (37.33)	3.39	0.06	1109 (36.25)	2178 (35.60)	1.36	0.54
Dyslipidemia (including hypercholesterolemia)	2103 (62.46)	31,221 (61.37)	2.24	0.21	1907 (62.34)	3798 (62.08)	0.54	0.81
Edema and fluid overload	404 (12.00)	6410 (12.60)	1.83	0.31	373 (12.19)	786 (12.85)	1.98	0.37
Hypertension	2339 (69.47)	37,180 (73.09)	8.00	< 0.0001	2157 (70.51)	4255 (69.55)	2.11	0.34
Renal disease	992 (29.46)	14,921 (29.33)	0.29	0.87	916 (29.94)	1756 (28.70)	2.73	0.22
Renal failure	581 (17.26)	11,901 (23.39)	15.30	< 0.0001	552 (18.05)	1077 (17.60)	1.15	0.60
Shortness of breath (excluding sleep apnea)	1362 (40.45)	21,056 (41.39)	1.91	0.28	1249 (40.83)	2502 (40.90)	0.13	0.95
Sleep apnea	619 (18.38)	7898 (15.53)	7.62	< 0.0001	556 (18.18)	1001 (16.36)	4.80	0.03

Table 3 continued

Characteristics	Before propensity score matching				After propensity score matching			
	New SAC/VAL users (*N* = 3367)	New ACEi/ARB users (*N* = 50,872)	SMD (%)	*P* value	New SAC/VAL users (*N* = 3059)	New ACEi/ARB users (*N* = 6118)	SMD (%)	*P* value
Cardiac-specific comorbidities, signs, symptoms, and devices, *n* (%)								
Angina pectoris	264 (7.84)	3415 (6.71)	4.34	0.01	233 (7.62)	440 (7.19)	1.62	0.46
Atrial fibrillation	1398 (41.52)	19,726 (38.78)	5.60	0.002	1254 (40.99)	2488 (40.67)	0.67	0.76
Cardiac arrhythmia (excluding atrial fibrillation)	1140 (33.86)	19,196 (37.73)	8.09	< 0.0001	1058 (34.59)	2135 (34.90)	0.65	0.77
Cardio-resynchronization therapy device	1226 (36.41)	10,333 (20.31)	36.30	< 0.0001	1010 (33.02)	2011 (32.87)	0.31	0.89
Cerebrovascular disease	349 (10.37)	7125 (14.01)	11.15	< 0.0001	327 (10.69)	639 (10.44)	0.80	0.72
Ischemic heart disease (including MI)	2240 (66.53)	34,331 (67.49)	2.04	0.25	2047 (66.92)	4000 (65.38)	3.25	0.14
Peripheral artery disease	190 (5.64)	3561 (7.00)	5.58	0.003	180 (5.88)	378 (6.18)	1.24	0.58
Peripheral vascular disease	329 (9.77)	5550 (10.91)	3.74	0.0396	306 (10)	592 (9.68)	1.10	0.62
Tachycardia	824 (24.47)	10,129 (19.91)	11.00	< 0.0001	721 (23.57)	1406 (22.98)	1.39	0.53
Valvular heart disease	1475 (43.81)	20,606 (40.51)	6.69	0.0002	1331 (43.51)	2661 (43.49)	0.03	0.99

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *COPD* chronic obstructive pulmonary disease, *ECI* Elixhauser Comorbidity Index, *ICD* International Classification of Diseases, *MI* myocardial infarction, *SAC/VAL* sacubitril/valsartan, *SMD* standardized mean difference

[a]ECI categorizes the comorbidities based on ICD diagnosis codes. The ECI score ranges from − 7 to 12 with higher scores indicating more severe symptom burden

were excluded from the analysis. For propensity matching, the most recent LVEF value (within the follow-up period) was used with hierarchical selection if multiple values were reported on the same day. All variables were included in the propensity score matching, regardless of the standardized mean difference (SMD) or *P* value.

Categorical variables are summarized as frequency counts and percentages and compared using the Chi-squared test. Continuous variables are summarized as *n*, mean, and standard deviation (SD) and compared using an unequal variance two-sample *t* test or the Mann–Whitney *U* test (for continuous variables with skewed

Table 4 Medication use before and after propensity score matching

Characteristics	Before propensity score matching				After propensity score matching			
	New SAC/VAL users (*N* = 3367)	New ACEi/ARB users (*N* = 50,872)	SMD (%)	*P* value	New SAC/VAL users (*N* = 3059)	New ACEi/ARB users (*N* = 6118)	SMD (%)	*P* value
Medications, *n* (%)								
Aldosterone antagonists	939 (27.89)	9823 (19.31)	20.31	< 0.0001	817 (26.71)	1637 (26.76)	0.11	0.96
Antiarrhythmics and digoxin	1792 (53.22)	33,856 (66.55)	27.45	< 0.0001	1704 (55.7)	3323 (54.32)	2.79	0.21
Beta-blockers	995 (29.55)	22,885 (44.99)	32.33	< 0.0001	966 (31.58)	1874 (30.63)	2.05	0.35
Calcium channel blockers	400 (11.88)	12,072 (23.73)	31.35	< 0.0001	397 (12.98)	841 (13.75)	2.26	0.31
Lipid-lowering drugs	1636 (48.59)	30,346 (59.65)	22.34	< 0.0001	1552 (50.74)	3101 (50.69)	0.10	0.96
Loop diuretics	2070 (61.48)	33,214 (65.29)	7.92	< 0.0001	1924 (62.9)	3782 (61.82)	2.23	0.32
Mineralocorticoid receptor antagonists	1105 (32.82)	13,388 (26.32)	14.28	< 0.0001	967 (31.61)	1974 (32.27)	1.40	0.53
Nitroglycerin	1700 (50.49)	31,938 (62.78)	24.99	< 0.0001	1614 (52.76)	3214 (52.53)	0.46	0.84

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *SAC/VAL* sacubitril/valsartan, *SMD* standardized mean difference

data). No imputation was performed for missing data.

A bivariate analysis was applied to the primary endpoint. All rate-of-event endpoints were modeled using a negative binomial model and the results are expressed as incidence rate ratios (IRRs) and 95% confidence intervals (CIs). Time-to-event outcomes were modeled using a subdistribution hazards model and the results are expressed as hazard ratios (HRs) and 95% CIs. The rate of HF-specific hospitalizations has significant competing risks of death and other hospitalizations. Therefore, a subdistribution hazards model was chosen over a Cox model as the former enables estimation of the incidence of event occurrence while taking competing risks into account, whereas the latter often overpredicts risk in scenarios with competing risks. For the purposes of this study, death and hospitalizations that were not of interest for any specific objective were accounted for as a competing risk within the subdistribution hazards model. The reliability of the results was assessed by replicating the results in both unadjusted and adjusted models. Variables that were significantly different between the cohorts after propensity score matching (i.e., those with an SMD $\geq$ 10% or $P < 0.1$) were further used for adjustment in the model for a perfectly matched sample.

RESULTS

Patient Characteristics

Overall, 3367 new SAC/VAL users and 50,872 new ACEi/ARB users met the study selection criteria (Fig. 2). The two cohorts differed in several patient characteristics before matching.

Table 5 Disease characteristics before and after propensity score matching

Characteristics	Before propensity score matching				After propensity score matching			
	New SAC/VAL users (*N* = 3367)	New ACEi/ARB users (*N* = 50,872)	SMD (%)	*P* value	New SAC/VAL users (*N* = 3059)	New ACEi/ARB users (*N* = 6118)	SMD (%)	*P* value
LVEF (%), mean (SD)	26.69 (8.15)	29.21 (8.21)	30.76	< 0.0001	27.06 (8.1)	27.06 (8.44)	0.12	0.84
Previous HF hospitalizations, *n* (%)								
0	2534 (75.26)	44,243 (86.97)	30.26	< 0.0001	2395 (78.29)	4839 (79.09)	1.96	0.69
1	543 (16.13)	4891 (9.61)	19.54		454 (14.84)	898 (14.68)	0.46	
2	153 (4.54)	1096 (2.15)	13.31		114 (3.73)	212 (3.47)	1.40	
3	64 (1.90)	322 (0.63)	11.35		44 (1.44)	69 (1.13)	2.76	
≥ 4	73 (2.17)	320 (0.63)	13.13		52 (1.7)	100 (1.63)	0.51	
Previous all-cause hospitalizations, *n* (%)								
0	1754 (52.09)	30,097 (59.16)	14.26	< 0.0001	1652 (54)	3337 (54.54)	1.08	0.87
1	739 (21.95)	11,109 (21.84)	0.27		678 (22.16)	1333 (21.79)	0.91	
2	358 (10.63)	4392 (8.63)	6.78		315 (10.3)	657 (10.74)	1.44	
3	204 (6.06)	2170 (4.27)	8.11		164 (5.36)	320 (5.23)	0.58	
≥ 4	312 (9.27)	3104 (6.10)	11.90		250 (8.17)	471 (7.70)	1.75	
Previous HF-specific outpatient visits, *n* (%)								
0	587 (17.43)	20,368 (40.04)	51.58	< 0.0001	587 (19.19)	1157 (18.91)	0.71	0.99
1	635 (18.86)	10,385 (20.41)	3.91		609 (19.91)	1217 (19.89)	0.04	
2	458 (13.60)	6137 (12.06)	4.60		429 (14.02)	857 (14.01)	0.05	
3	372 (11.05)	3777 (7.42)	12.54		325 (10.62)	667 (10.90)	0.90	
≥ 4	1315 (39.06)	10,205 (20.06)	42.56		1109 (36.25)	2220 (36.29)	0.07	
Previous HF-specific ER visits, *n* (%)								
0	3182 (94.51)	49,313 (96.94)	12.03	< 0.0001	2902 (94.87)	5852 (95.65)	3.69	0.34
1	154 (4.57)	1356 (2.67)	10.23		129 (4.22)	224 (3.66)	2.86	
2	19 (0.56)	153 (0.30)	4.02		19 (0.62)	33 (0.54)	1.08	
3	4 (0.12)	32 (0.06)	1.86		4 (0.13)	5 (0.08)	1.51	
≥ 4	8 (0.24)	18 (0.04)	5.48		5 (0.16)	4 (0.07)	2.90	

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ER* emergency room, *HF* heart failure, *LVEF* left ventricular ejection fraction, *SAC/VAL* sacubitril/valsartan, *SMD* standardized mean difference

Notably, compared with new ACEi/ARB users, new SAC/VAL users were younger; had a higher proportion of men (Table 2); a higher proportion of patients with tachycardia and cardiac resynchronization therapy; a lower proportion of patients with cerebrovascular

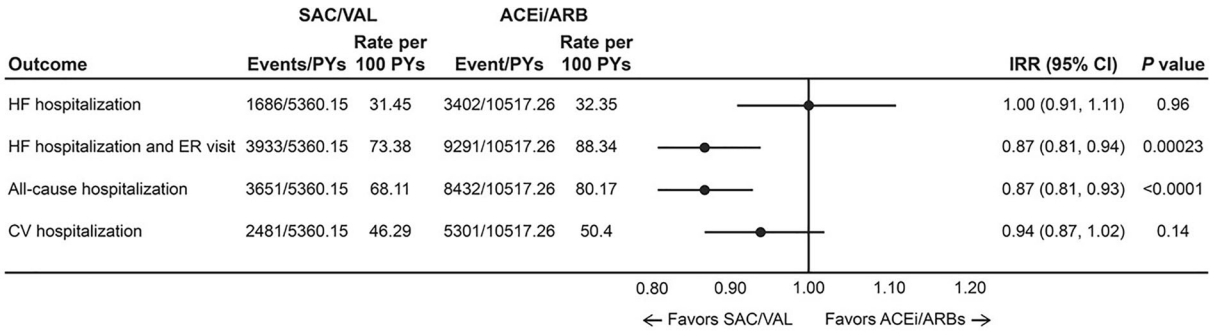

Fig. 3 Comparison of rate of events between new SAC/VAL users and new ACEi/ARB users. *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CI* confidence interval, *CV* cardiovascular, *ER* emergency room, *HF* heart failure, *IRR* incidence rate ratio, *PY* patient-year, *SAC/VAL* sacubitril/valsartan

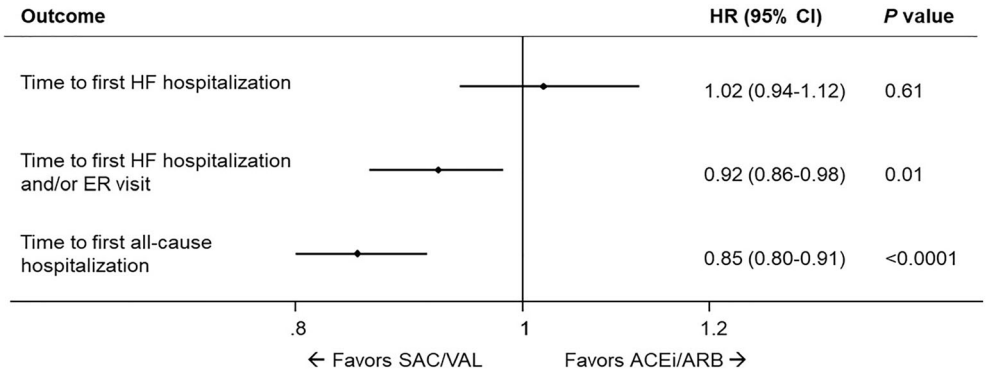

Fig. 4 Comparison of time to event between new SAC/VAL users and new ACEi/ARB users. *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CI* confidence interval, *ER* emergency room, *HF* heart failure, *HR* hazard ratio, *SAC/VAL* sacubitril/valsartan

disease, renal failure, dementia, and altered consciousness (Table 3); a lower proportion of patients with prior medication use (except for aldosterone antagonists and mineraloreceptor antagonists, Table 4); a lower mean LVEF; and a higher proportion of patients with HF hospitalizations, all-cause hospitalizations, HF-specific outpatient visits, and HF-specific ER visits in the previous year suggestive of more severe HF in the SAC/VAL cohort (Table 5).

Propensity score matching could be performed for 91% of new SAC/VAL users and 12% of new ACEi/ARB users. After propensity score matching, there were 3059 patients in the SAC/VAL cohort and 6118 patients in the ACEi/ARB cohort, with no significant differences between the two cohorts for any of the baseline characteristics except the proportion of patients with sleep apnea, which was higher in the SAC/VAL cohort (18.2 vs. 16.4%; $P = 0.03$). Baseline characteristics of the two groups after propensity score matching are presented in Tables 2, 3, 4 and 5. More than 80% of patients had at least one HF-specific outpatient visit and approximately 46% of patients had at least one all-cause hospitalization during the 365-day pre-index period. Approximately 21% of patients had at least one HF hospitalization during the 365-day pre-index period, whereas 5% had at least one HF-specific ER visit.

Post-index Hospitalization

The rates of events during the follow-up period are summarized in Fig. 3. The rate of post-index HF hospitalizations was similar between new SAC/VAL users and new ACEi/ARB users (31.45 per 100 person-years [PYs] vs. 32.35 per 100 PYs, respectively; IRR 1.00; 95% CI 0.91–1.11; $P = 0.96$). The rate of all-cause hospitalization was 13% lower for new SAC/VAL users compared with new ACEi/ARB users (68.11 per 100 PYs vs. 80.17 per 100 PYs; IRR 0.87; 95% CI 0.81–0.93; $P < 0.0001$). Similarly, the rate of the composite of HF hospitalization or ER visits was 13% lower for new SAC/VAL users compared with new ACEi/ARB users (73.38 per 100 PYs vs. 88.34 per 100 PYs; IRR 0.87; 95% CI 0.81–0.94; $P = 0.00023$). The rate of cardiovascular hospitalizations was similar between the two cohorts (46.29 per 100 PYs vs. 50.40 per 100 PYs; IRR 0.94; 95% CI 0.87–1.02; $P = 0.14$).

The time-to-event analysis showed similar results, with new SAC/VAL users having a significantly lower risk of first HF hospitalization or ER visit (HR 0.92; 95% CI 0.86–0.98; $P = 0.01$) and first all-cause hospitalization (HR 0.85; 95% CI 0.80–0.91; $P < 0.0001$) compared with new ACEi/ARB users (Fig. 4). The results were similar to those estimated using the unadjusted model (results not presented).

DISCUSSION

The new SAC/VAL users in this study had significantly lower rates of all-cause hospitalizations and the composite of HF hospitalization or ER visits than the new ACEi/ARB users; this was true in the analyses of both total rates and time to first event. These results were similar to those observed in a systematic literature review of real-world studies, wherein studies comparing SAC/VAL with ACEi/ARB in patients with HFrEF (previously treated or naïve to ACEi/ARB) reported a significantly lower risk of all-cause hospitalization with SAC/VAL [20].

Despite significant differences in the rate of all-cause hospitalization, the rates of HF and cardiovascular hospitalizations were similar between new SAC/VAL users and new ACEi/ARB users—an initially unexpected and clinically counterintuitive finding. However, another US-based real-world study by Tan et al. [17] involving patients with systolic HF observed a similar pattern—a significantly lower risk for all-cause hospitalization in the SAC/VAL group than in the ACEi/ARB group ($P < 0.001$), but not for HF hospitalization ($P = 0.26$). Tan et al. considered that differences in coding practices could have influenced the analysis of HF-specific hospitalizations. As was done in the Tan et al. study, we also defined HF hospitalization per ICD-9-CM and ICD-10-CM codes for HF listed within the primary diagnoses associated with a hospitalization. Although the rate of HF hospitalizations was similar between treatment groups, a composite endpoint of HF hospitalization or ER visits did show a significant difference between SAC/VAL and ACEi/ARB, indicating that ACEi/ARB-treated patients are more likely to present to the ER for their HF than SAC/VAL-treated patients. Analyzing emergency visits that do not result in a hospitalization in addition to hospital admissions, may provide a complete picture of the burden of HF-related events to the healthcare system rather than focusing on hospitalizations alone. Moreover, all-cause hospitalization is considered more important by payers and patients than cause-specific hospitalization, as it represents the overall disease burden [21].

Frequent hospitalizations pose a major burden on patients with HF and their caregivers. In addition, consistent evidence indicates that the economic burden of HF is dominated by the hospitalization costs [11, 16, 22, 23]. A US-based analysis found that inpatient costs accounted for 80% of the total lifetime costs in HF [24]. Therefore, we expect that the reduction in all-cause hospitalizations observed among the new SAC/VAL users in our study will be meaningful in reducing the overall burden of hospitalizations for patients. Reducing the risk of total hospitalizations due to any cause is of particular importance in the context of the current coronavirus disease 2019 (COVID-19) pandemic, when it is imperative to keep patients out of hospital.

To the best of our knowledge, the present study is the first real-world study to specifically

compare SAC/VAL and ACEi/ARB use in patients with HFrEF naïve to prior RAASi therapy. Previous subgroup analyses have shown that the benefit of SAC/VAL is similar in patients naïve to ACEi/ARB and those pretreated with ACEi/ARB [9, 17]. A subgroup analysis of a US administrative claims database study showed a similar reduction in all-cause hospitalization with SAC/VAL in patients who were previously treated with ACEi/ARB and those naïve to ACEi/ARB [17]. In a sub analysis of the PIONEER-HF trial, the superiority of SAC/VAL over enalapril was consistent in patients with or without prior exposure to ACEi/ARB [9, 10]. The time to onset of HF hospitalization for the PIONEER-HF trial and the present real-world study were different (PIONEER-HF: HR 0.61, 95% CI 0.40, 0.93; present study: HR 0.92, 95% CI 0.80, 0.91). However, it is important to note that time frame investigated in the present study is much longer than the 8-week time frame in PIONEER-HF trial. Due to the nature of the data and the varying index dates in the present study, we defined the follow-up period as until end of the study period (March 31, 2020), death or patient transfer out of the database. Therefore, in the present study, patients could potentially be assessed for time to HF hospitalization over a period greater than 3 years.

Our findings of the real-world benefit of SAC/VAL on all-cause hospitalizations in patients naïve to prior RAASi therapy are consistent with the results from these previous subgroup analyses and support the use of SAC/VAL in this patient population. Moreover, the recent update of the ACC ECDP for optimization of HF treatment has now recommended a "direct-to-ARNI approach," that is to use ARNI as a de novo RAASi therapy in patients naïve to ACEi/ARB therapy [6].

The findings of the present study should be interpreted in light of several limitations. Because of the retrospective, observational nature of the study, the causal relationships between the clinical outcomes and the treatment could not be inferred. Medication use might have been overestimated because the drug prescription was used as a proxy for drug use. Therefore, it was not possible to determine whether the patients used their medication as prescribed. The use of SAC/VAL or ACEi/ARB may be influenced by the socioeconomic status of a patient. However, this parameter could not be adjusted as details on socioeconomic status were not available in Optum EHRs. Despite matching several key patient characteristics between the SAC/VAL and ACEi/ARB incident cohorts, a possibility of imbalances in the disease severity might exist, with a chance that patients with more persistent symptoms may have been prescribed SAC/VAL. Possibility of differences in the disease severity might be due to the non-availability of some of the variables, including NYHA class, blood pressure, and biomarkers (e.g., N-terminal pro-B-type natriuretic peptide and renal function markers). Another limitation was that the "naïve" populations in the study were defined as "being naïve to ACEi/ARB and SAC/VAL for at least 365 days before the initial prescription for either ACEi/ARB or SAC/VAL". Although it was unlikely that patients were previously treated with SAC/VAL because of the overlapping of the identification period of our study with the date of licensing of SAC/VAL in the US, it could have been possible that an individual might not be "truly" naïve to ACEi/ARB and had merely not been prescribed ACEi/ARB during the 365 days before their index prescription within the database. Lastly, the results of this study may not be generalized to other populations, such as the new SAC/VAL and new ACEi/ARB users who were excluded from the analysis during propensity score matching, those with different ethnicity or from different regions, and those who were uninsured or on fee-for-service healthcare plans.

CONCLUSIONS

Use of SAC/VAL in RAASi-naïve patients with HFrEF resulted in lower rates of all-cause hospitalization and the composite of HF hospitalization or ER visits compared with ACEi/ARB treatment. The rates of HF and cardiovascular hospitalizations were similar between the two cohorts. These findings further strengthen the evidence base for SAC/VAL in ACEi/ARB-naïve

patients. Initiating SAC/VAL directly in RAASi-naïve patients with HFrEF can reduce total hospitalizations, thereby reducing the clinical and economic burden of HFrEF in these patients.

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Compliance with Ethics Guidelines. Institutional review board approval was not required for this study because the information retrieved from the database was de-identified.

Data Availability. The data from the Optum EHR database are currently licensed and accessible within Novartis via the EVIdence of OutComes (EVICO) platform.

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