ORIGINAL RESEARCH

Lower Hospitalization and Healthcare Costs With Sacubitril/Valsartan Versus Angiotensin-Converting Enzyme Inhibitor or Angiotensin-Receptor Blocker in a Retrospective Analysis of Patients With Heart Failure

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***Background*—**Outcomes data among patients with heart failure (HF) with reduced ejection fraction treated with sacubitril/valsartan (SAC/VAL) are largely limited to clinical trial results. We compared hospitalization and healthcare costs among real-world patients with HF with reduced ejection fraction treated with SAC/VAL versus angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker (ACEI/ARB).

***Methods and Results*—**Using retrospective administrative claims data, stable patients with HF with reduced ejection fraction treated with SAC/VAL or ACEI/ARB from October 2015 to June 2016 were identified. Postindex hospitalization and healthcare costs were assessed in propensity-matched cohorts using robust variance estimation. Time to first hospitalization was modeled using unadjusted Kaplan–Meier estimates and multivariable models. Postindex all-cause healthcare costs were modeled using an adjusted multivariable model. Among 279 patients per matched cohort, postindex hospitalization risk was lower for SAC/VAL compared with ACEI/ARB using Kaplan–Meier estimation and unadjusted Cox models. For HF hospitalization, the hazard ratio (95% CI) was 0.56 (0.33–0.94; *P*=0.030). Adjusted results were similar to unadjusted. Mean (SD) monthly healthcare costs were lower for SAC/VAL versus ACEI/ARB for all categories except pharmacy, with hospital costs being particularly disparate between cohorts: for HF hospitalization, $248 ($1588) for SAC/VAL versus $1122 ($7290) for ACEI/ARB. The adjusted risk of incurring increased all-cause postindex costs was lower for SAC/VAL versus ACEI/ARB (cost ratio [95% CI] 0.74 [0.59–0.94]; *P*=0.013).

***Conclusions*—**In clinical practice, patients with HF with reduced ejection fraction treated with SAC/VAL were less likely to be hospitalized than matched patients treated with ACEI/ARB. Despite higher pharmacy costs, SAC/VAL–treated patients incurred lower monthly medical and total healthcare costs. **(*J Am Heart Assoc*. 2019;8:e011089. DOI: 10.1161/JAHA.118.011089.)**

Key Words: healthcare costs • heart failure • hospitalization • retrospective studies • sacubitril/valsartan

Heart failure (HF) is a major cause of morbidity and mortality; as recently as 2014, ≈900 000 hospital discharges for HF occurred in the United States.[1] The cost associated with HF—estimated at $31 billion in 2012—is forecasted to increase to $70 billion by 2030, driven by an aging population and epidemiological factors such as obesity, hypertension, diabetes mellitus, and coronary artery disease.[2,3]

Although HF is poised to remain a heavy burden on the US healthcare system for years to come, in recent decades pharmacological therapy enhancements have reduced morbidity and mortality among patients with HF with reduced ejection fraction (HFrEF).[4] Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) improve clinical outcomes in HFrEF[4] and were the mainstays of HFrEF renin-angiotensin system blockade therapy until 2015, when sacubitril/valsartan (SAC/VAL), a combination neprilysin inhibitor and ARB, was approved by the US Food and Drug Administration. SAC/VAL is used in patients with chronic HFrEF and New York Heart Association functional class II to IV symptoms. Approval of SAC/VAL was based largely on the strength of results from the PARADIGM-HF

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Clinical Perspective

What Is New?

- In real-world clinical practice settings, patients with heart failure with reduced ejection fraction treated with sacubitril/valsartan were less likely to be hospitalized than patients treated with an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker after controlling for patient demographics, comorbid conditions, and other factors.
- Patients treated with sacubitril/valsartan also had lower hospitalization costs and total all-cause healthcare costs than those treated with angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker.

What Are the Clinical Implications?

- Cost is often implicated as a barrier to use of novel pharmacological therapy for heart failure with reduced ejection fraction; however, in our real-world analysis, increased pharmacy costs for sacubitril/valsartan –treated patients were mitigated by lower medical costs.
- Healthcare providers need to consider clinical benefit and total costs in addition to drug costs when making treatment decisions.

(Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, in which SAC/VAL reduced the risk of cardiovascular death and first HF hospitalization among patients with HFrEF by 20% compared with the ACEI, enalapril.[5,6] Reducing hospitalization risk is critical, given that HF hospitalization has been associated with higher 30- to 60-day mortality and readmission rates[7] and accounts for the majority of costs attributable to HF in the United States.[8]

Although PARADIGM-HF illustrated superior efficacy of SAC/VAL compared with enalapril in a clinical trial setting,[6] real-world data regarding outcomes associated with SAC/VAL use—including potential economic benefit—are limited. This study was conducted to compare hospitalization and healthcare costs among stable patients with HFrEF treated with SAC/VAL versus an ACEI or ARB in clinical practice.

Methods

Study Design and Data Sources

Research materials, data, and analytical methods will not be made available to other researchers for purposes of replicating analysis procedures or reproducing study results.

This retrospective study was conducted using administrative claims data from October 1, 2014 through September 30, 2016 from the Optum Research Database (ORD) with merged mortality data from the US Social Security Administration public death master file. The ORD is a large, population-representative database containing de-identified medical and pharmacy claims data and linked enrollment information for individuals enrolled in US commercial and Medicare Advantage health plans. Medical claims included diagnosis and procedure codes from the *International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification* (*ICD-9-CM* and *ICD-10-CM*); Current Procedural Terminology or Healthcare Common Procedure Coding System codes; site of service codes; paid amounts; and other information. Pharmacy claims included drug name, dosage form, drug strength, fill date, number of days' supply, and financial information for health plan–provided outpatient pharmacy services. Because no identifiable protected health information was accessed during this study, institutional review board approval or waiver of authorization was not required.

Patient Identification and Cohort Assignment

The study included patients with at least 1 pharmacy claim for SAC/VAL, ACEI, or ARB from October 1, 2015 through June 30, 2016 (identification period). Adults with a claim for SAC/VAL during the identification period and no previous claims for SAC/VAL were assigned to the SAC/VAL cohort, and those with a claim for ACEI or ARB during the identification period and no claims for SAC/VAL from July 7, 2015 (market approval) through September 30, 2016 (end of the study period) were assigned to the ACEI/ARB cohort. The date of the first claim for the index therapy was defined as the index date. Continuous enrollment in the health plan with both medical and pharmacy coverage was required during the 12 months preceding the index date (preindex period) and for a minimum 3-month postindex period starting on the index date and ending on the earliest of the following: end of the study period, health plan disenrollment, or death.

Included patients were required to have claims evidence of HFrEF and a stable clinical status. Criteria for claims evidence of HFrEF and stable status are given in Figure 1.[9] Patients were also required to be aged ≥18 years (and <65 years if they had a commercial health plan) and to have no missing demographic data. Finally, in order to control for possible early differences in days' supply of the index therapy (eg, 30- versus 90-day supply) between cohorts, only patients with proportion of days covered ≥0.80 in the first 3 months of the postindex period were retained in the study sample.

To account for potential selection bias, cohorts were 1:1 propensity-score matched on selected demographics and preindex patient characteristics (see Table 1), including exact matching on health plan type (commercial or Medicare

Claims evidence of HFrEF (at least 1 of the following):
At least 1 non–rule-out claim with a diagnosis code for systolic HF in any position (ICD-9-CM 428.2x, 428.4x; ICD-10-CM I50.2*, I50.4*) during the preindex period or on the index date At least 1 non–rule-out claim with a diagnosis code for unspecified HF in any position (ICD-9-CM 428.0, 428.1, 428.9; ICD-10-CM I50.1, I50.9) during the preindex period or on the index date and meeting 1 of the following additional criteria: – At least 1 non–rule-out claim with a diagnosis code for cardiomyopathy in any position (ICD-9-CM 414.8, 425.2, 425.5, 425.7, 425.8; ICD-10-CM I25.5, I42.0, I42.6, I42.7) during the preindex period or on the index date – A least 1 inpatient hospital facility claim with a diagnosis code for ST-segment elevation myocardial infarction in any position (ICD-9-CM 410.0x, 410.1x, 410.2x, 410.3x, 410.4x, 410.5x, 410.6x; ICD-10-CM I21.0*, I21.1*, I21.2*, I21.3, I22.0, I22.1, I22.8, I22.9) during the preindex period – At least 1 medical claim with a procedure code for cardiac resynchronization therapy or implantable cardioverter defibrillator (HCPCS/CPT 33223, 33224, 33225, 33226, 33230, 33231, 33240, 33241, 33243, 33244, 33245, 33246, 33249, 33262, 33263, 33264, 33270, 33271, 33272, 33273, 93260, 93261, 93282, 93283, 93284, 93287, 93289, 93295, 93640, 93641, 93642, 93644, 0319T, 0320T, 0321T, 0322T, 0323T, 0324T, 0325T, 0326T, 0327T, 0328T, C1721, C1722, C1777, C1882, C1895, C1896, C1899, G0448; ICD-10-PCS 02H4*JZ, 02H4*KZ, 02H6*KZ, 02H7*KZ, 02HK*KZ, 02HL*JZ, 02HL*KZ, 02HL3MZ, 02HN*KZ, 0JH607Z, 0JH608Z, 0JH609Z, 0JH637Z, 0JH638Z, 0JH639Z, 0JH807Z, 0JH808Z, 0JH809Z, 0JH837Z, 0JH838Z, 0JH839Z, 4B02XTZ; ICD-9-CM 00.50, 00.51, 00.52, 00.53, 00.54, 37.94, 37.95, 37.96, 37.97, 37.98, 89.49) during the preindex period or on the index date
Claims evidence of stable status (all of the following):
No medical claims with codes for heart valve surgery, percutaneous coronary intervention, coronary artery bypass graft, cardiorespiratory failure and shock, or parenteral inotropic therapy within 6 weeks prior to the index date[9]
No skilled nursing facility stays or other inpatient stays (eg, hospice) within 6 weeks prior to the index date
No inpatient hospital stays overlapping the index date
No medical claims with codes for mechanical circulatory support, heart transplant, dementia, human immunodeficiency virus infection, AIDS, moderate or severe liver disease, or metastatic solid tumor within 12 months prior to the index date
No evidence of pregnancy, labor, or delivery from October 1, 2014 through September 30, 2016

Figure 1. Criteria for claims evidence of HFrEF and stable status. Rule-out claims (diagnostic services claims) included medical claims with a diagnosis code and diagnostic service procedure code(s) without any other services. Non–rule-out claims represented medical claims other than rule-out claims. AIDS indicates acquired immunodeficiency syndrome; CPT, current procedural terminology; HCPCS, Healthcare Common Procedure Coding System; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; *ICD-9-CM*, *International Classification of Diseases, Ninth Edition, Clinical Modification*; *ICD-10-CM*, *International Classification of Diseases, Tenth Edition, Clinical Modification*.

Advantage). For each patient in the SAC/VAL cohort, a patient in the ACEI/ARB cohort with the closest propensity score within a caliper of 0.20 of the SD of the estimated logit was selected. Unmatched patients were excluded from the analysis.

Patient Characteristics and Outcomes

Patient characteristics included demographic information (age, sex, health plan type, and geographical region); duration of the postindex period; preindex Quan–Charlson comorbidity score;[10] selected preindex comorbid conditions, signs and symptoms (based on *ICD-9-CM* or *ICD-10-CM* diagnosis codes), preindex HF-related outpatient pharmacotherapy (ACEI/ARB, evidence-based beta blocker, mineralocorticoid receptor agonist, loop diuretic, thiazide diuretic, and digoxin); selected preindex other outpatient pharmacotherapy (anticoagulant, antiplatelet agent, nondihydropyridine calcium-channel blocker, dihydropyridine calcium-channel blocker, lipid-altering medication, vasodilator, insulin, or noninsulin hypoglycemic agent); number of preindex HF-related guideline therapies (ACEI/ARB, evidence-based beta blocker, mineralocorticoid receptor agonist, isosorbide dinitrate+hydralazine, digoxin, and ivabradine); preindex cardiac resynchronization

Table 1. Patient Characteristics

Characteristic	SAC/VAL Cohort (n=279)	ACEI/ARB Cohort (n=279)	*P* Value	Used for Match*	Prematch SMD (%)	Postmatch SMD (%)
Age, y, mean (SD)	68.2 (12.4)	67.6 (12.9)	0.400	✓†	−29.78	5.51
Male, n (%)	192 (68.8)	188 (67.4)	0.720	✓	14.94	3.02
Medicare Advantage health plan, n (%)	205 (73.5)	205 (73.5)	…	✓	−25.68	−0.00
Geographical region, n (%)			0.786	✓	5.20	−5.31
Northeast	54 (19.4)	45 (16.1)	0.313	✓	6.92	8.36
Midwest	77 (27.6)	82 (29.4)	0.630	✓	−23.93	−3.85
South	129 (46.2)	133 (47.7)	0.726	Ref.	19.77	−2.92
West	19 (6.8)	19 (6.8)	1.000	✓	−4.46	0.00
Duration of postindex period, days, mean (SD)	186.9 (69.2)	183.0 (71.2)	0.352	✓†	−177.2	5.82
Selected preindex comorbid conditions, n (%)‡						
Hypertension	256 (91.8)	251 (90.0)	0.457		0.51	6.33
Dyslipidemia (including hypercholesterolemia)	226 (81.0)	221 (79.2)	0.584	✓	1.29	4.56
Ischemic heart disease (including MI)	215 (77.1)	200 (71.7)	0.137		11.77	12.34
Diabetes mellitus (including complications)	156 (55.9)	157 (56.3)	0.932	✓	12.54	−0.72
Atrial fibrillation	125 (44.8)	132 (47.3)	0.545		4.56	−5.05
Renal disease	89 (31.9)	93 (33.3)	0.703		1.06	−3.08
Chronic obstructive pulmonary disease	76 (27.2)	82 (29.4)	0.581		−4.08	−4.76
Sleep apnea	74 (26.5)	70 (25.1)	0.708	✓	16.22	3.39
Anemia (including iron deficiency)	37 (13.3)	42 (15.1)	0.530		1.44	−5.27
Selected preindex signs and symptoms, n (%)‡						
Shortness of breath (not including sleep apnea)	228 (81.7)	230 (82.4)	0.823	✓	31.47	−1.67
Altered consciousness	103 (36.9)	118 (42.3)	0.188		−0.68	−11.10
Tachycardia	88 (31.5)	93 (33.3)	0.653	✓	17.04	−3.98
Edema and fluid overload	60 (21.5)	72 (25.8)	0.232	✓	−5.20	−10.32
Pulmonary edema	38 (13.6)	36 (12.9)	0.803	✓	11.29	2.23
Number of preindex guideline-recommended therapies,§ n (%)						
0	7 (2.5)	2 (0.7)	0.097		−8.83	10.16
1	23 (8.2)	28 (10.0)	0.447		−41.19	−5.08
2	92 (33.0)	98 (35.1)	0.591		−28.14	−4.44
3	109 (39.1)	105 (37.6)	0.730		35.95	3.15
4	45 (16.1)	42 (15.1)	0.722		39.81	3.54
5	3 (1.1)	4 (1.4)	0.706		14.42	−4.12
Preindex CRT/ICD, n (%)	172 (61.6)	157 (56.3)	0.163	✓	55.33	11.15
Preindex HF hospitalization, n (%)	66 (23.7)	64 (22.9)	0.835	✓†	27.10	1.85
Preindex all-cause hospitalization, n (%)	124 (44.4)	136 (48.7)	0.312		0.24	−8.65

ACEI/ARB indicates angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; CRT/ICD, cardiac resynchronization therapy or implantable cardioverter-defibrillator; HF, heart failure; ref., reference; MI, myocardial infarction; SAC/VAL, sacubitril/valsartan; SMD, standardized mean difference.

*In addition to the patient characteristics indicated, SAC/VAL and ACEI/ARB cohorts were matched for preindex Quan–Charlson comorbidity score (category), selected preindex comorbid conditions (ischemic heart disease [other than MI], pulmonary vascular disease, peripheral artery disease, liver disease, anxiety [including adjustment disorders with anxiety], and substance abuse/dependence [including drugs and alcohol]), preindex HF-related outpatient pharmacotherapy (ACEI/ARB, evidence-based beta blocker, mineralocorticoid receptor agonist, loop diuretic, thiazide diuretic, and digoxin), selected preindex other outpatient pharmacotherapy (anticoagulant, antiplatelet agent, nondihydropyridine calcium-channel blocker, dihydropyridine calcium-channel blocker, lipid-altering medication, vasodilator, insulin, and noninsulin hypoglycemic agent), preindex revascularization, preindex all-cause medical and pharmacy costs (health plan–dependent quintiles), and encounter with cardiologist in the month preindex. Each preindex outpatient pharmacotherapy was calculated as total days' supply.

†Match performed using categorical version.

‡Identified using *ICD-9-CM* and *ICD-10-CM* diagnosis codes.

§Guideline-recommended medical therapies included ACEI/ARB, evidence-based beta blocker, mineralocorticoid receptor agonist, isosorbide dinitrate+hydralazine, digoxin, and ivabradine.

therapy or implantable cardioverter defibrillator; preindex revascularization; preindex hospitalization (all-cause and HF); preindex all-cause medical costs; preindex all-cause outpatient pharmacy costs; and encounter with cardiologist in the month preindex. HF hospitalization was identified on the basis of facility claims for hospitalizations with an HF diagnosis code (*ICD-9-CM* 402.x1, 404.x1, 404.x3, 428.xx; *ICD-10-CM* I11.0, I13.0, I13.2, I50.1, I50.2*, I50.3*, I50.4*, I50.9, I97.13*) in the primary position.

Study outcomes included postindex hospitalization (HF and all-cause; measured as per-patient-per-month [PPPM] count, indicator variable, and time to first event) and healthcare costs (HF hospital and all-cause; measured as PPPM costs). HF hospital costs were defined as costs associated with HF hospitalization. Healthcare costs were calculated as combined health plan plus patient-paid amounts, adjusted to 2016 US dollars using the annual medical care component of the Consumer Price Index.[11] Patient-paid amounts were also calculated separately. All-cause healthcare costs were reported as total costs and for subcategories of medical, hospital, and outpatient pharmacy costs.

Statistical Analysis

The pre- and postmatch balances of patient characteristics between cohorts were evaluated using standardized mean differences (SMDs; by convention, values ≥10% indicated meaningful imbalance).[12] Postindex hospitalization (PPPM counts) and healthcare costs between matched cohorts were compared using robust variance estimation. Time to first postindex hospitalization (HF and all-cause) was modeled using Kaplan–Meier failure probability estimates and multivariable Cox proportional hazards models. Postindex all-cause healthcare costs were modeled using a multivariable generalized linear model with gamma distribution and log link. In addition to cohort, adjustment variables for multivariable modeling included age and health plan type interaction, sex, selected (a priori) preindex chronic comorbid conditions, selected (a priori) preindex signs and symptoms, number of preindex guideline therapies, preindex cardiac resynchronization therapy/implantable cardioverter defibrillator, preindex revascularization, preindex HF hospitalization, preindex all-cause medical costs, and preindex all-cause outpatient pharmacy costs. Because the precision of signs/symptoms identified from *ICD-9/10-CM* codes may vary, sensitivity analyses in which preindex signs and symptoms were excluded from the multivariable models were also performed. Statistical analysis was performed using SAS software (version 9.4; SAS Institute Inc, Cary, NC). $P<0.05$ was considered statistically significant.

Results

Study Sample

Among patients who initiated 1 of the index therapies during the identification period, the remaining selection criteria were satisfied by 287 in the SAC/VAL cohort and 22 469 in the ACEI/ARB cohort (Figure 2). Before matching, several patient characteristics differed between cohorts. Compared with ACEI/ARB–treated patients, SAC/VAL–treated patients were younger (mean age, 68.0 versus 71.6 years; SMD=−29.8); had a higher percentage of commercial enrollees (26.8% versus 16.3%; SMD=25.7); had a lower mean duration of the postindex period (185 versus 303 days; SMD=−177.2); had higher percentages of selected preindex comorbid conditions and symptoms, including pulmonary vascular disease (15.3% versus 7.6%; SMD=24.4) and shortness of breath (81.5% versus 68.0%; SMD=31.5); and had a higher percentage with preindex HF hospitalization (24.0% versus 13.5%; SMD=27.10; Table 1).

After propensity-score matching, there were 279 patients in each cohort. Preindex characteristics were similar for SAC/VAL versus ACEI/ARB and SMDs were ≤10% for most variables (range, 0.0–12.5%), although differences remained for ischemic heart disease (77.1% versus 71.7%; SMD=12.3), altered consciousness (36.9% versus 42.3%; SMD=−11.1), and edema and fluid overload (21.5% versus 25.8%; SMD=−10.3). Other preindex comorbid conditions that were highly prevalent though similar between cohorts included hypertension (91.8% SAC/VAL, 90.0% ACEI/ARB), dyslipidemia (81.0% SAC/VAL, 79.2% ACEI/ARB), diabetes mellitus (55.9% SAC/VAL, 56.3% ACEI/ARB), and atrial fibrillation (44.8% SAC/VAL, 47.3% ACEI/ARB).

Postindex Hospitalization

Mean (SD) number of postindex PPPM hospitalizations was lower in the SAC/VAL versus the ACEI/ARB cohort for HF hospitalizations (0.01 [0.06] versus 0.03 [0.10]; $P=0.003$) and all-cause hospitalizations (0.05 [0.11] versus 0.11 [0.20]; $P<0.001$). Kaplan–Meier estimation revealed a lower probability of first postindex HF hospitalization and all-cause hospitalization with SAC/VAL versus ACEI/ARB at 30, 91, and 183 days (Figure 3). Risk-based postindex hospitalization in unadjusted Cox proportional hazards models was also lower among SAC/VAL–treated versus ACEI/ARB–treated patients (HF hospitalization hazard ratio [HR], 0.56; 95% CI, 0.33–0.94; $P=0.030$ and all-cause hospitalization HR, 0.57; 95% CI, 0.42–0.77; $P<0.001$). Multivariable analysis results were similar after adjustment for preindex demographics and characteristics (HF hospitalization HR, 0.42; 95% CI, 0.23–0.79; $P=0.007$ and all-cause hospitalization HR, 0.51; 95% CI, 0.36–0.71; $P<0.001$; Tables 2 and 3, respectively). In sensitivity analyses that excluded signs and symptoms from the

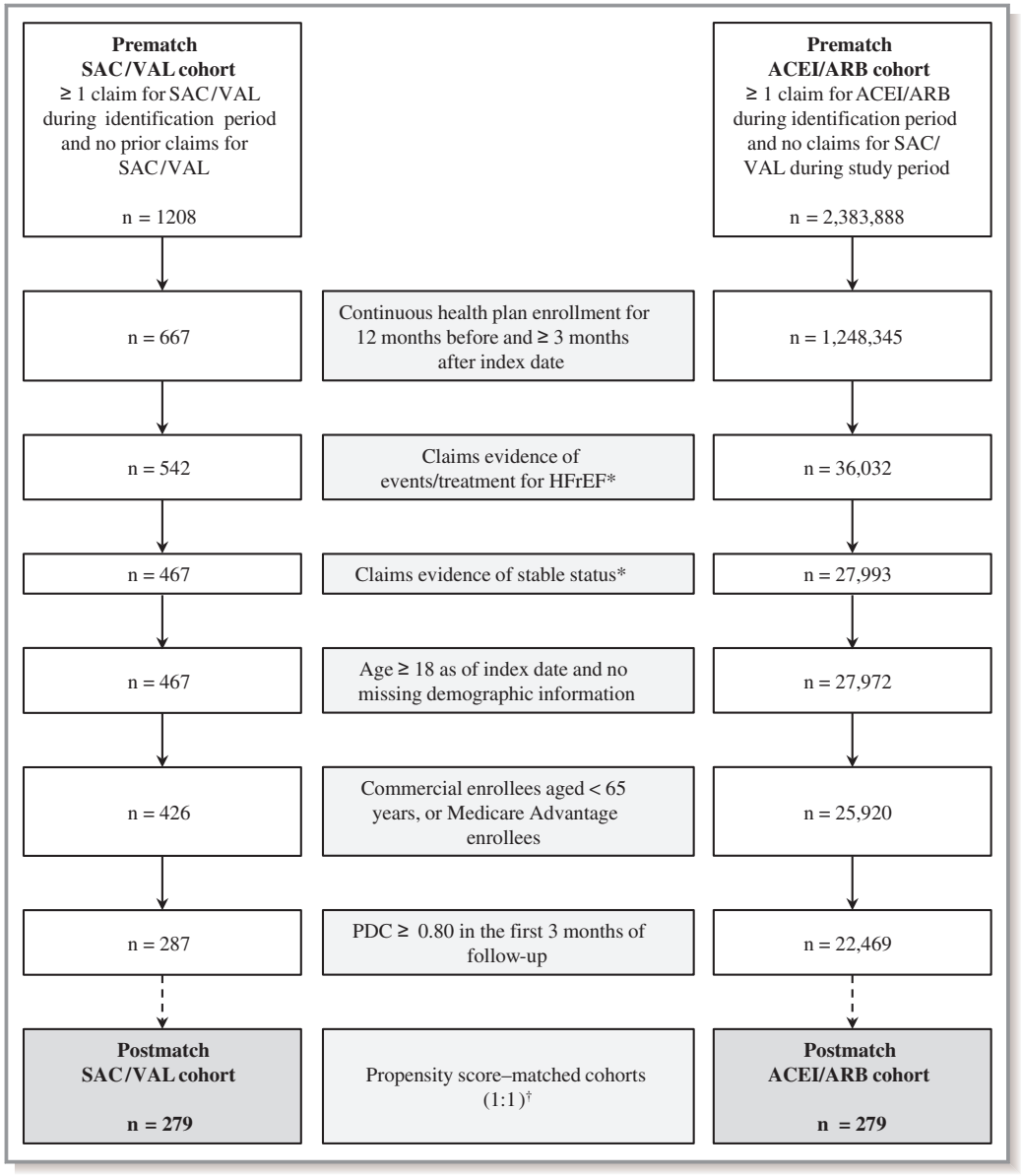
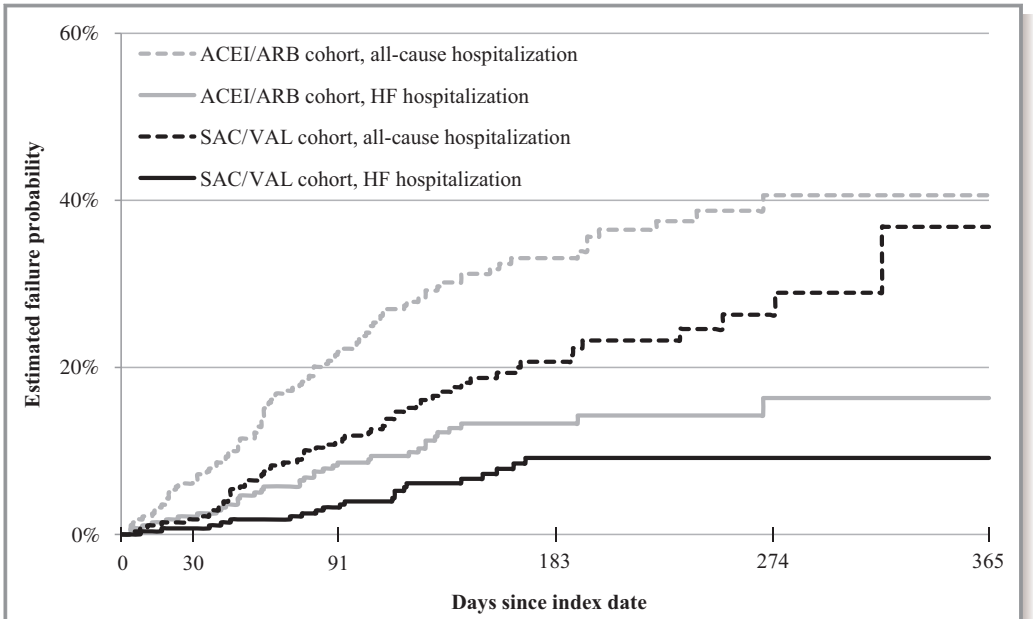


Figure 2. Patient selection and attrition. Identification period: October 1, 2015 through June 30, 2016. Index date: date of first pharmacy claim for SAC/VAL or ACEI/ARB. ACEI/ARB indicates angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; CRT/ICD, cardiac resynchronization therapy/implantable cardioverter-defibrillator; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction; PDC, proportion of days covered; SAC/VAL, sacubitril/valsartan. *Criteria for claims evidence of HF and stable status are provided in Figure 1. †Variables used in propensity score matching are provided in Table 1.

multivariable models, adjusted hospitalization risk remained lower for patients treated with SAC/VAL compared with ACEI/ARB (HF hospitalization HR, 0.43; 95% CI, 0.24–0.80; P=0.007 and all-cause hospitalization HR, 0.50; 95% CI, 0.36–0.69; P<0.001; full results not shown).

Postindex Healthcare Costs

Patients treated with SAC/VAL had lower postindex PPPM HF hospital costs (P=0.048), all-cause total costs (P=0.033), all-cause medical costs (P=0.004), and all-cause hospital costs (P<0.001) compared with patients treated with ACEI/ARB (Figure 4, health plan–paid plus patient-paid). Patients treated with ACEI/ARB versus SAC/VAL had mean (SD) PPPM costs that were >4 times higher for HF hospitalization ($1122 [$7290] versus $248 [$1588]; P=0.048) and >3 times higher for all-cause hospitalization ($2770 [$9189] versus ($810 [$2921]; P<0.001). Mean (SD) PPPM all-cause outpatient pharmacy costs were higher for SAC/VAL compared with ACEI/ARB ($947 [$1282] versus $515 [$1041];



	Estimated failure probability, % (patients at risk)		
	30 days	91 days	183 days
SAC/VAL cohort			
HF hospitalization	0.7 (277)	3.2 (270)	9.2 (117)
All-cause hospitalization	1.8 (274)	11.1 (248)	20.7 (101)
ACEI/ARB cohort			
HF hospitalization	2.2 (273)	8.6 (256)	13.3 (100)
All-cause hospitalization	6.5 (262)	21.9 (219)	33.1 (88)

Figure 3. Kaplan–Meier plots of first postindex hospitalization. Patient data are observed until each event of interest (HF hospitalization or all-cause hospitalization) or patient postindex is censored (earliest of end of study period, health plan disenrollment, or death). Log-rank tests: P=0.031 for HF hospitalization; P<0.001 for all-cause hospitalization (SAC/VAL cohort vs ACEI/ARB cohort). ACEI/ARB indicates angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; HF, heart failure; SAC/VAL, sacubitril/valsartan.

P<0.001). After adjusting for preindex demographics and characteristics, risk of incurring increased total PPPM costs was lower for patients treated with SAC/VAL compared with ACEI/ARB (cost ratio [95% CI] 0.74 [0.59–0.94]; P=0.013; Table 4). When a sensitivity analysis excluding signs and symptoms from the multivariable model was performed, adjusted risk remained lower for patients treated with SAC/VAL compared with ACEI/ARB (cost ratio [95% CI] 0.71 [0.56–0.90]; P=0.004; full results not shown).

The impact on patient-paid costs was similar to that observed for overall costs. Compared with ACEI/ARB–treated patients, those treated with SAC/VAL had lower postindex PPPM patient-paid HF hospital costs (P=0.023), all-cause total costs (P=0.023), all-cause medical costs (P<0.001), and all-cause hospital costs (P<0.001), but higher postindex PPPM all-cause outpatient pharmacy costs (P<0.001; Figure 4).

Discussion

In this real-world analysis, patients with HFrEF treated with SAC/VAL in clinical practice were less likely to be hospitalized and incurred lower total healthcare costs than those treated with ACEI/ARB. Our results provide an important complement to those of PARADIGM-HF, in which SAC/VAL was superior to enalapril for reducing cardiovascular death and first HF hospitalization in a clinical trial setting.[6] Real-world data regarding longitudinal health economic outcomes among patients with HFrEF who were treated with SAC/VAL have been reported in only 1 other article to date, a single-arm report by Antol et al.[13] The substantial reduction in hospitalization observed in our study's SAC/VAL cohort was congruent with findings from the Antol et al study, which involved enrollees in health plans managed by Humana (primarily Medicare Advantage). After initiating SAC/VAL, patients had a

Table 2. Multivariable Proportional Hazards Model of Follow-up HF Hospitalization

Independent Variable	Hazard Ratio (95% CI)	*P* Value
SAC/VAL cohort (ref.: ACEI/ARB cohort)*	0.42 (0.23–0.79)	0.007
Health plan type, patient age (ref.: commercial, 18–64 y)		
Medicare Advantage, 18 to 64 y	2.48 (0.79–7.78)	0.119
Medicare Advantage, ≥65 y	2.50 (0.89–7.08)	0.084
Male (ref.: female)	0.65 (0.33–1.25)	0.196
Baseline comorbid conditions		
Dyslipidemia	0.63 (0.29–1.35)	0.231
Ischemic heart disease other than MI	2.93 (1.13–7.61)	0.027
Diabetes mellitus (including complications)	0.73 (0.37–1.46)	0.377
Atrial fibrillation	1.67 (0.87–3.20)	0.122
Renal disease	1.57 (0.76–3.23)	0.224
Chronic obstructive pulmonary disease	0.68 (0.36–1.32)	0.257
Peripheral artery disease	0.96 (0.43–2.17)	0.924
Cerebrovascular disease	0.73 (0.27–1.95)	0.529
Pulmonary edema	0.45 (0.17–1.17)	0.103
Asthma	0.95 (0.41–2.19)	0.906
Pulmonary vascular disease	0.85 (0.35–2.07)	0.712
Primary malignancy	1.74 (0.74–4.12)	0.205
Liver disease	1.38 (0.41–4.64)	0.600
Baseline symptoms		
Shortness of breath	2.27 (0.76–6.73)	0.141
Altered consciousness	0.71 (0.33–1.54)	0.383
Tachycardia	1.58 (0.85–2.94)	0.145
Edema and fluid overload	1.68 (0.81–3.51)	0.167
Palpitations	1.35 (0.62–2.95)	0.454
Baseline number of HF guideline-recommended therapies† (ref.: 0–1)		
2	5.77 (1.08–30.96)	0.041
3	3.82 (0.75–19.56)	0.108
≥4	6.27 (1.16–33.92)	0.033
Baseline CRT/ICD	2.33 (1.18–4.57)	0.014
Baseline revascularization	0.32 (0.07–1.38)	0.125
Baseline HF hospitalizations (ref.: 0)		
1	3.09 (1.24–7.74)	0.016
≥2	11.22 (3.50–35.95)	<0.001
Baseline all-cause medical costs‡ (ref.: quintile 1)		
Quintile 2	2.07 (0.78–5.50)	0.147
Quintile 3	1.14 (0.36–3.54)	0.827
Quintile 4	1.19 (0.41–3.42)	0.751
Quintile 5	0.68 (0.21–2.22)	0.527
Baseline all-cause outpatient pharmacy costs‡ (ref.: quintile 1)		
Quintile 2	0.61 (0.19–1.95)	0.406
Quintile 3	0.87 (0.30–2.51)	0.789
Quintile 4	1.77 (0.66–4.74)	0.256
Quintile 5	1.05 (0.36–3.01)	0.931

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CRT/ICD, cardiac resynchronization therapy+implantable cardioverter defibrillator; HF, heart failure; MI, myocardial infarction; ref., reference; SAC/VAL, sacubitril/valsartan.

*Unadjusted results for HF hospitalization: hazard ratio=0.56; 95% CI, 0.33 to 0.94; *P*=0.030.

†Guideline therapies include ACEI/ARB, evidence-based beta blocker, mineralocorticoid receptor antagonist, hydralazine+isosorbide dinitrate, digoxin, and ivabradine.

‡Health plan–dependent quintiles; quintiles are ordered from 1 (lowest cost) to 5 (highest cost).

decrease in 3-month all-cause hospitalization, from 27.5% to 17.0%.[13] Hospitalization is an important outcome in HFrEF; it is widespread,[14] and patients who are hospitalized are highly likely to be readmitted.[8,15] In a 2017 analysis, more than 40% of Medicare beneficiaries hospitalized for HF were readmitted within 90 days.[15] Given that hospitalization is a robust predictor of increased mortality in the HFrEF population,[7] reduction of inpatient admissions is essential to improving patient morbidity and mortality outcomes.

In this study, total postindex HF hospital costs and all-cause total healthcare costs were lower for patients treated with SAC/VAL versus ACEI/ARB. Despite strong evidence of superior efficacy, adoption of SAC/VAL in clinical practice after US market approval has been relatively slow, with reports ranging from 2%[16] to 13%[17] of patients with HFrEF. Cost has often been implicated as a barrier to use of novel pharmacological therapy, because both health plan– and patient-paid costs for new drugs are considerably higher than those for established HFrEF guideline therapies.[16,18,19] In 2016, the estimated monthly retail cost of treatment with SAC/VAL was $425 compared with $9 and $25 for lisinopril and enalapril, respectively,[19] and in a retrospective analysis using 2015–2016 data from the OptumLabs Data Warehouse, patient-paid monthly costs for SAC/VAL remained high—a mean of $71 compared with $2 to $3 for lisinopril, losartan, carvedilol, and spironolactone—despite the majority of monthly costs being covered by payers.[16] Our findings offer new evidence that SAC/VAL provides value in terms of healthcare costs (HF hospital, all-cause total, all-cause medical, and all-cause hospital). Perceptions surrounding drug cost should be balanced with clinical and total cost benefits. Similar to other analyses of real-world data for SAC/VAL, our results reflect an early view (the first 15 months

Table 3. Multivariable Proportional Hazards Model of Follow-up All-Cause Hospitalization

Independent Variable	Hazard Ratio (95% CI)	*P* Value
SAC/VAL cohort (ref.: ACEI/ARB cohort)*	0.51 (0.36–0.71)	<0.001
Health plan type, patient age (ref.: commercial, 18–64 y)		
Medicare Advantage, 18 to 64 y	2.12 (1.13–3.98)	0.020
Medicare Advantage, ≥65 y	1.96 (1.08–3.56)	0.028
Male (ref.: female)	0.89 (0.62–1.28)	0.536
Baseline comorbid conditions		
Dyslipidemia	0.92 (0.58–1.47)	0.723
Ischemic heart disease other than MI	1.69 (1.01–2.81)	0.044
Diabetes mellitus (including complications)	0.99 (0.66–1.47)	0.944
Atrial fibrillation	1.16 (0.82–1.63)	0.414
Renal disease	1.66 (1.12–2.45)	0.012
Chronic obstructive pulmonary disease	0.74 (0.50–1.11)	0.142
Peripheral artery disease	0.75 (0.46–1.22)	0.241
Cerebrovascular disease	0.95 (0.60–1.49)	0.812
Pulmonary edema	0.81 (0.49–1.35)	0.422
Asthma	1.24 (0.80–1.94)	0.338
Pulmonary vascular disease	1.00 (0.60–1.67)	0.992
Primary malignancy	1.60 (0.98–2.62)	0.059
Liver disease	0.84 (0.46–1.55)	0.580
Baseline symptoms		
Shortness of breath	2.10 (1.11–3.98)	0.023
Altered consciousness	1.07 (0.75–1.52)	0.717
Tachycardia	1.19 (0.83–1.71)	0.340
Edema and fluid overload	1.52 (1.01–2.29)	0.047
Palpitations	0.71 (0.39–1.30)	0.264
Baseline number of HF guideline-recommended therapies† (ref.: 0–1)		
2	1.31 (0.72–2.38)	0.382
3	0.99 (0.52–1.86)	0.963
≥4	1.45 (0.76–2.77)	0.259
Baseline CRT/ICD	1.18 (0.80–1.73)	0.408
Baseline revascularization	1.32 (0.78–2.23)	0.300
Baseline HF hospitalizations (ref.: 0)		
1	1.24 (0.75–2.07)	0.402
≥2	2.59 (1.37–4.91)	0.004
Baseline all-cause medical costs‡ (ref.: quintile 1)		
Quintile 2	1.48 (0.75–2.90)	0.259
Quintile 3	1.18 (0.64–2.17)	0.607
Quintile 4	1.10 (0.56–2.16)	0.791
Quintile 5	1.45 (0.72–2.93)	0.296
Baseline all-cause outpatient pharmacy costs‡ (ref.: quintile 1)		
Quintile 2	0.88 (0.46–1.69)	0.701
Quintile 3	1.11 (0.62–2.01)	0.721
Quintile 4	1.63 (0.91–2.94)	0.102
Quintile 5	1.49 (0.79–2.84)	0.221

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CRT/ICD, cardiac resynchronization therapy+implantable cardioverter defibrillator; HF, heart failure; MI, myocardial infarction; ref., reference; SAC/VAL, sacubitril/valsartan.

*Unadjusted results for all-cause hospitalization: hazard ratio=0.57; 95% CI, 0.42 to 0.77; $P<0.001$.

†Guideline therapies include ACEI/ARB, evidence-based beta blocker, mineralocorticoid receptor antagonist, hydralazine+isosorbide dinitrate, digoxin, and ivabradine.

‡Health plan–dependent quintiles; quintiles are ordered from 1 (lowest cost) to 5 (highest cost).

after US Food and Drug Administration approval) of patient access to this therapy. As additional evidence of clinical practice outcomes becomes available and SAC/VAL is increasingly accepted by the healthcare community, its accessibility and affordability may change markedly.

In our analysis, and congruent with existing data, both combined and patient-paid outpatient pharmacy costs were higher for SAC/VAL compared with ACEI/ARB. Higher drug costs were offset by reduced monthly medical costs; in particular, hospital costs and total healthcare costs were lower in the SAC/VAL cohort. Our real-world results provide further evidence that the economic burden of HF is dominated by inpatient costs. In 1 report, inpatient costs accounted for as much as 62% of total healthcare costs.[15] Economic modeling analyses using data from PARADIGM-HF consistently indicated that treating HFrEF with SAC/VAL compared with enalapril would be cost-effective from a US payer perspective.[20–23] The present report expands on current knowledge by examining cost from a patient perspective. Interestingly, our finding that total healthcare costs were lower for SAC/VAL initiators contrasts with findings from modeling analyses, in which researchers suggested that increased quality-adjusted life-years associated with SAC/VAL use among patients with HFrEF would come with higher healthcare costs.[20–23] Possible explanations for this discrepancy include differences in event rates between our patient sample and the PARADIGM-HF study sample, as well as our use of actual paid amounts rather than modeled cost data. Our results contribute to the body of literature and can be utilized to help make future cost-effectiveness analyses more reflective of real-world patient outcomes.

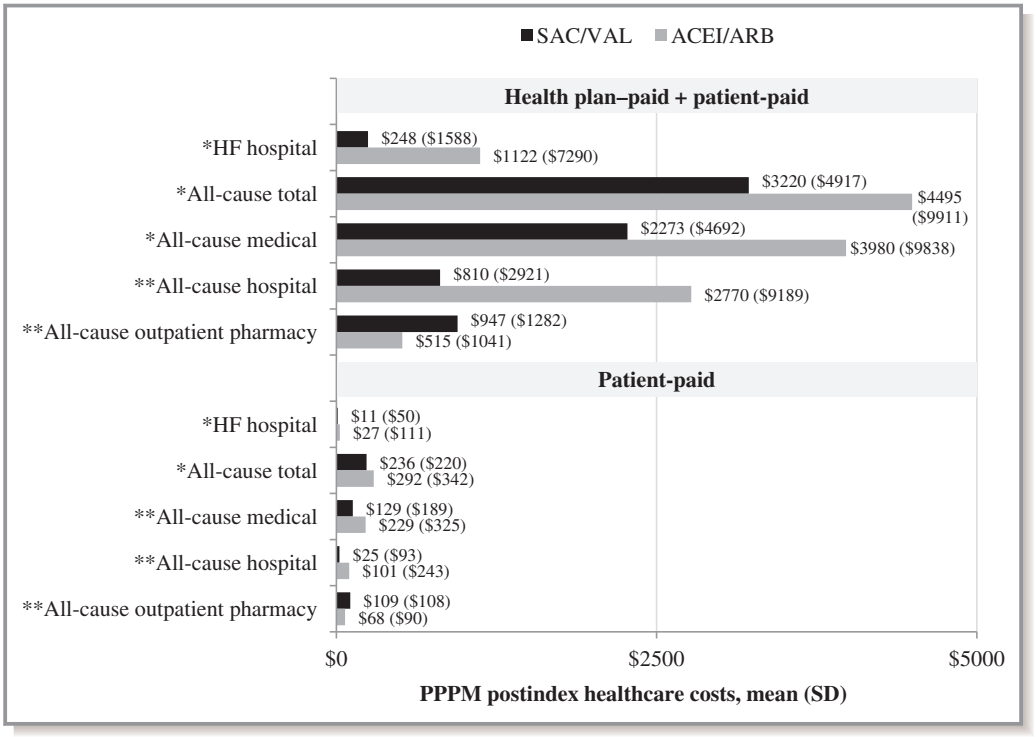


Figure 4. Per-patient per-month (PPPM) postindex healthcare costs. Combined health plan–paid+patient-paid amounts (top) and patient-paid amounts (bottom) are shown. *P<0.05; **P<0.001. ACEI/ARB indicates angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; HF, heart failure; SAC/VAL, sacubitril/valsartan.

Data regarding real-world characteristics among patients with HFrEF who were treated with SAC/VAL were found in only 3 articles: by Antol et al,[13] a single-arm, retrospective, medical record–augmented data claims study of 200 US patients initiating SAC/VAL between August 2015 and March 2016; by Wachter et al,[24] an electronic medical records–based study of 1041 German patients initiating SAC/VAL in 2016; and from the authors of the Change in Management of Patients with Heart Failure (CHAMP-HF) registry,[17] a prospective longitudinal study of 3497 US patients, 452 of which were prescribed SAC/VAL. Patients in claims- and electronic medical records–based samples, compared with patients from trials and registries, were older (mean age, 68, 72, 73, 64, and 66 years for the current study, Antol et al, Wachter et al, the PARADIGM-HF clinical trial, and the CHAMP-HF registry, respectively) and had a higher comorbidity burden, including higher percentages with hypertension (92%, 94%, 56%, 71%, and 82%), diabetes mellitus (56%, 53%, 31% [exception, lower percentage], 34%, and 41%), and atrial fibrillation (45%, 48%, 29% [atrial fibrillation/flutter; exception, lower percentage], 37%, and 36%).

It was not surprising that the PARADIGM-HF sample was younger and healthier than our real-world sample of patients with HFrEF, given that clinical trials are often conducted among individuals with stable non-HF preindex characteristics. For example, in 2 reports of hospitalized adults, a retrospective review of patient characteristics showed that only 55%[25] and 45%[26] of patients who were US Food and Drug Administration-eligible for SAC/VAL would have met the PARADIGM-HF inclusion criteria. Retrospectively obtained real-world data from patients initiating SAC/VAL have been similar to those in a contemporary non–SAC/VAL real-world report of patients with HFrEF,[15] and reflect that real-world patients with chronic HF may have more age-related and medical challenges that could influence clinical outcomes over time. Thus, there is a need to examine data from clinically complex cohorts that are representative of patients treated in clinical practice following publication of clinical trial results.

Study Limitations

Our findings should be interpreted in light of several limitations. Because this was a retrospective observational study, causal relationships cannot be inferred between the outcomes of interest and treatment with SAC/VAL or ACEI/ARB. Furthermore, the potential impact of concomitant HF-related therapies was not examined, and other unmeasured variables, such as drug dosage, patient socioeconomic status, or provider performance metrics, may have also affected the results. This study was conducted in a US managed-care

Table 4. Multivariable Generalized Linear Model of Follow-up All-Cause Healthcare Costs

Independent Variable	Hazard Ratio (95% CI)	*P* Value
SAC/VAL cohort (ref.: ACEI/ARB cohort)	0.74 (0.59–0.94)	0.013
Health plan type, patient age (ref.: commercial, 18–64 y)		
Medicare Advantage, 18 to 64 y	0.97 (0.59–1.59)	0.890
Medicare Advantage, ≥65 y	0.72 (0.50–1.04)	0.081
Male (ref.: female)	0.95 (0.71–1.26)	0.705
Baseline comorbid conditions		
Dyslipidemia	0.90 (0.58–1.42)	0.660
Ischemic heart disease other than MI	1.24 (0.86–1.78)	0.256
Diabetes mellitus (including complications)	0.73 (0.55–0.97)	0.031
Atrial fibrillation	1.02 (0.77–1.34)	0.902
Renal disease	1.13 (0.82–1.55)	0.451
Chronic obstructive pulmonary disease	1.01 (0.73–1.40)	0.948
Peripheral artery disease	0.91 (0.67–1.22)	0.514
Cerebrovascular disease	0.90 (0.68–1.19)	0.456
Pulmonary edema	0.80 (0.47–1.36)	0.404
Asthma	0.81 (0.57–1.15)	0.228
Pulmonary vascular disease	1.12 (0.81–1.56)	0.499
Primary malignancy	1.06 (0.74–1.52)	0.745
Liver disease	0.95 (0.66–1.38)	0.789
Baseline symptoms		
Shortness of breath	1.25 (0.87–1.79)	0.232
Altered consciousness	1.00 (0.76–1.32)	0.987
Tachycardia	0.98 (0.77–1.26)	0.886
Edema and fluid overload	1.33 (0.91–1.93)	0.139
Palpitations	1.33 (0.78–2.26)	0.300
Baseline number of HF guideline recommended therapies* (ref.: 0–1)		
2	1.23 (0.74–2.05)	0.425
3	1.12 (0.71–1.77)	0.637
≥4	1.54 (0.94–2.54)	0.090
Baseline CRT/ICD	0.98 (0.76–1.27)	0.885
Baseline revascularization	0.76 (0.50–1.15)	0.195
Baseline HF hospitalizations (ref.: 0)		
1	1.35 (0.93–1.98)	0.119
≥2	1.17 (0.70–1.96)	0.554
Baseline all-cause medical costs† (ref.: quintile 1)		
Quintile 2	1.33 (0.88–2.01)	0.181
Quintile 3	1.48 (0.98–2.24)	0.066
Quintile 4	1.72 (1.07–2.77)	0.025
Quintile 5	2.12 (1.25–3.58)	0.005
Baseline all-cause outpatient pharmacy costs† (ref.: quintile 1)		
Quintile 2	1.23 (0.79–1.94)	0.362
Quintile 3	0.95 (0.62–1.46)	0.824
Quintile 4	1.30 (0.82–2.04)	0.263
Quintile 5	1.96 (1.21–3.19)	0.007

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CRT/ICD, cardiac resynchronization therapy+implantable cardioverter defibrillator; HF, heart failure; MI, myocardial infarction; ref., reference; SAC/VAL, sacubitril/valsartan.

*Guideline therapies include ACEI/ARB, evidence-based beta blocker, mineralocorticoid receptor antagonist, hydralazine+isosorbide dinitrate, digoxin, ivabradine.

†Health plan–dependent quintiles; quintiles are ordered from 1 (lowest cost) to 5 (highest cost).

sample, and the mean length of the postindex period was 6 months. Results may not be generalizable to other populations, such as patients who are uninsured or on fee-for-service healthcare plans, and may be most relevant in the short-term period following SAC/VAL (versus ACEI/ARB) initiation. Patients in the cohorts were matched at a 1:1 ratio, which limited the precision of estimators; however, a 1:1 ratio was chosen to reduce bias in estimators to the greatest possible extent. In addition, some small between-cohort differences in several preindex patient characteristics remained after matching. Although the list of match variables was extensive, it is also possible that there were between-cohort imbalances in disease severity that were not evident in the observed patient characteristics, particularly given that the diagnosis codes used to identify signs and symptoms can be imprecise and do not capture stability or severity, and patients with more-persistent symptoms may have been more likely to initiate SAC/VAL. Because this study used claims data, we recognize inherent limitations; most important, pharmacy claims reflected medication fills, not over-the-counter drug use, physician-provided samples, fills not processed through the primary insurer (eg, medications available through low-cost generic programs), or medications prescribed but not filled. In addition, presence of a diagnosis code on a medical claim does not assure the presence of disease, given that diagnoses may be coded incorrectly or included as rule-out criteria. Conversely, identification of conditions and signs and symptoms based on diagnosis codes requires that they were actually coded. Some information is not available in claims data, such as New York Heart Association functional class, ejection fraction percentage, blood pressure, and results from testing of serum electrolytes and biomarkers (eg, potassium, renal function markers, and

N-terminal pro-B-type natriuretic peptide). Finally, a proxy algorithm was used to help identify patients with HFrEF.

Conclusion

Among patients with HFrEF, treatment with SAC/VAL in clinical practice was associated with lower short-term postindex hospitalization risk and total healthcare costs compared with treatment with ACEI/ARB. Increased pharmacy costs for SAC/VAL–treated patients were mitigated by lower medical costs, including HF and all-cause hospital costs. These findings underscore the need to consider clinical benefit and total costs in addition to drug costs when making treatment decisions. Treatment of real-world patients with SAC/VAL has the potential to improve clinical outcomes and reduce the economic burden of HFrEF.

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