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ORIGINAL RESEARCH

Use and Out-of-Pocket Cost of Sacubitril-Valsartan in Patients With Heart Failure

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BACKGROUND: Current guidelines recommend use of sacubitril-valsartan in patients with heart failure with reduced ejection fraction (HFrEF). Early data suggested low uptake of sacubitril-valsartan, but contemporary data on real-world use and their associated cost are limited.

METHODS AND RESULTS: This was a retrospective study of individuals enrolled in Optum Clinformatics, a national insurance claims data set from 2016 to 2018. We included all adult patients with HFrEF with 2 outpatient encounters or 1 inpatient encounter with an *International Classification of Diseases, Tenth Revision* (*ICD-10*), diagnosis of HFrEF and 6 months of continuous enrollment, also receiving β-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers within 6 months of HFrEF diagnosis. We included 70 245 patients with HFrEF, and 5217 patients (7.4%) received sacubitril-valsartan prescriptions. Patients receiving care through a cardiologist compared with a primary care physician alone were more likely to receive sacubitril-valsartan (odds ratio, 1.61 [95% CI, 1.52–1.71]). Monthly out-of-pocket (OOP) cost for sacubitril-valsartan, compared with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, was higher for both commercially insured patients (mean, $69 versus $6.74) and Medicare Advantage (mean, $62 versus $2.52). For patients with commercial insurance, OOP cost was lower in 2016 than in 2018. For patients with Medicare Advantage, there was a significant geographic variation in the OOP costs across the country, ranging from $31 to $68 per month across different regions, holding all other patient-related factors constant.

CONCLUSIONS: Sacubitril-valsartan use was infrequent among patients with HFrEF. Patients receiving care with a cardiologist were more likely to receive sacubitril-valsartan. OOP costs remain high, potentially limiting use. Significant geographic variation in OOP costs, unexplained by patient factors, was noted.

Key Words: adult ■ angiotensin receptor blocker-neprilysin inhibitor ■ health expenditure ■ heart failure with reduced ejection fraction ■ humans ■ retrospective studies ■ sacubitril-valsartan

Guideline-directed medical therapy using angiotensin antagonists in addition to β-blockers has been the standard of care for patients with heart failure with reduced ejection fraction (HFrEF) for >2 decades.[1] In 2014, there was a paradigm shift in guideline-directed medical therapy for HFrEF because of a clinical trial that showed combination of an angiotensin receptor blocker and neprilysin inhibitor (ARNI) was superior to angiotensin-converting enzyme (ACE) inhibitors in patients with HFrEF.[2] At present, sacubitril-valsartan is the only ARNI available, and its use is endorsed as a class I recommendation over other angiotensin antagonists in patients with HFrEF by all major cardiovascular societies.[3,4] Although early reports showed slow uptake of sacubitril-valsartan in this population,[5,6] there is a paucity of longitudinal studies assessing uptake over time.

Slow and uneven adoption of novel agents may be attributable to several reasons. First, patient-level factors could play a key role, including nonclinical factors related to access to care that may exacerbate well-established race and sex differences, as noted with other therapies for HFrEF.[7,8] Second, system-level

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CLINICAL PERSPECTIVE

What Is New?

- In a large, claims data set, use of sacubitril-valsartan was low, at 7.4%, among patients with heart failure with reduced ejection fraction between 2016 and 2018; and involvement of a cardiologist in care was the only modifiable factor associated with higher rates of its use.
- Monthly out-of-pocket cost for sacubitril-valsartan, compared with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, was higher for both commercially insured patients (mean, $69 versus $6.74) and Medicare Advantage (mean, $62 versus $2.52) with significant geographic variation in the out-of-pocket costs.

What Are the Clinical Implications?

- Increased education on use of sacubitril-valsartan as well as legislative efforts to reduce drug costs are needed.

Nonstandard Abbreviations and Acronyms

ARNI	angiotensin receptor blocker and neprilysin inhibitor
HFrEF	heart failure with reduced ejection fraction
OOP	out of pocket

factors, like high out-of-pocket (OOP) costs for patients, lack of a formulary alternative, or lengthy prior authorization process, may play a role for novel agents.[9,10] This has been described previously with ARNI therapy as well because alternatives, such as ACE inhibitors, are substantially cheaper.[6] Specific factors associated with high OOP cost for ARNI, including its trend over time, are not known. In addition, whether geographic variation in OOP costs exist for ARNI, similar to other medications, has not been evaluated.[11] Identifying both patient- and systems-level factors would enable identifying individuals at risk for not receiving guideline-directed medical therapy for HFrEF, facilitating targeted cost reduction or assistance.

Accordingly, we aimed to examine rates and predictors of ARNI use and identify patients at risk for financial burden and medication nonadherence because of high OOP costs associated with this medication. More specifically, we first describe factors associated with ARNI use from 2016 to 2018 in a large cohort of patients with HFrEF from a national insurance claims data set. Next, we assessed OOP cost for patients and examined factors associated with high OOP cost for ARNI. Finally, we reported geographic variation across the United States in OOP cost for ARNI therapy.

METHODS

Data Sources

Optum Clinformatics Data Mart is a deidentified database of administrative health claims of >80 million commercially insured beneficiaries enrolled in private and Medicare Advantage health plans.[12] The database comprises inpatient and outpatient claims for all enrolled individuals in all 50 states. It also includes pharmacy claims data on outpatient prescription medication coverage for enrolled individuals with medical and pharmacy coverage. As patient-level data are deidentified, the study was determined to be exempt by the University of Michigan Institutional Review Board. Statistical codes for analyses are available from the authors and will be posted on github at the time of publication.

Study Design, Setting, and Population

This is a retrospective cohort study of individuals enrolled in the Optum Clinformatics Data Mart from January 1, 2016, to December 31, 2018. We included all individuals aged ≥18 years, with at least 2 outpatient encounters or 1 inpatient encounter with *International Classification of Diseases, Tenth Revision (ICD-10)*, codes for HFrEF (Table S1). These billing codes have been previously validated with a specificity of 97.7% in identifying patients with heart failure (HF) with an ejection fraction of <45%. To further identify patients with HFrEF, we only included individuals who received prescriptions for β-blockers and ACE inhibitors/angiotensin receptor blockers (ARBs) using the National Drug Codes for outpatient pharmacy refills presented at the time or within 6 months before index date. Index date for the study cohort was the date of first HFrEF billing code within the specified time period. We required all individuals to have continuous enrollment in a medical and prescription drug plan for at least 6 months before their index date. We also required all individuals to have continuous enrollment for at least 1 month after their index date to avoid including patients who change insurances after receiving a diagnosis of HF. Figure 1 summarizes the inclusion and exclusion criteria for our cohort creation. For our cost analysis, we restricted our analysis to individuals with prescriptions of at least 30 days' supply after the index date.

Variables

Exposure Variables

Variables of interest included patient demographics, comorbidities, and other HF prescriptions. Patient

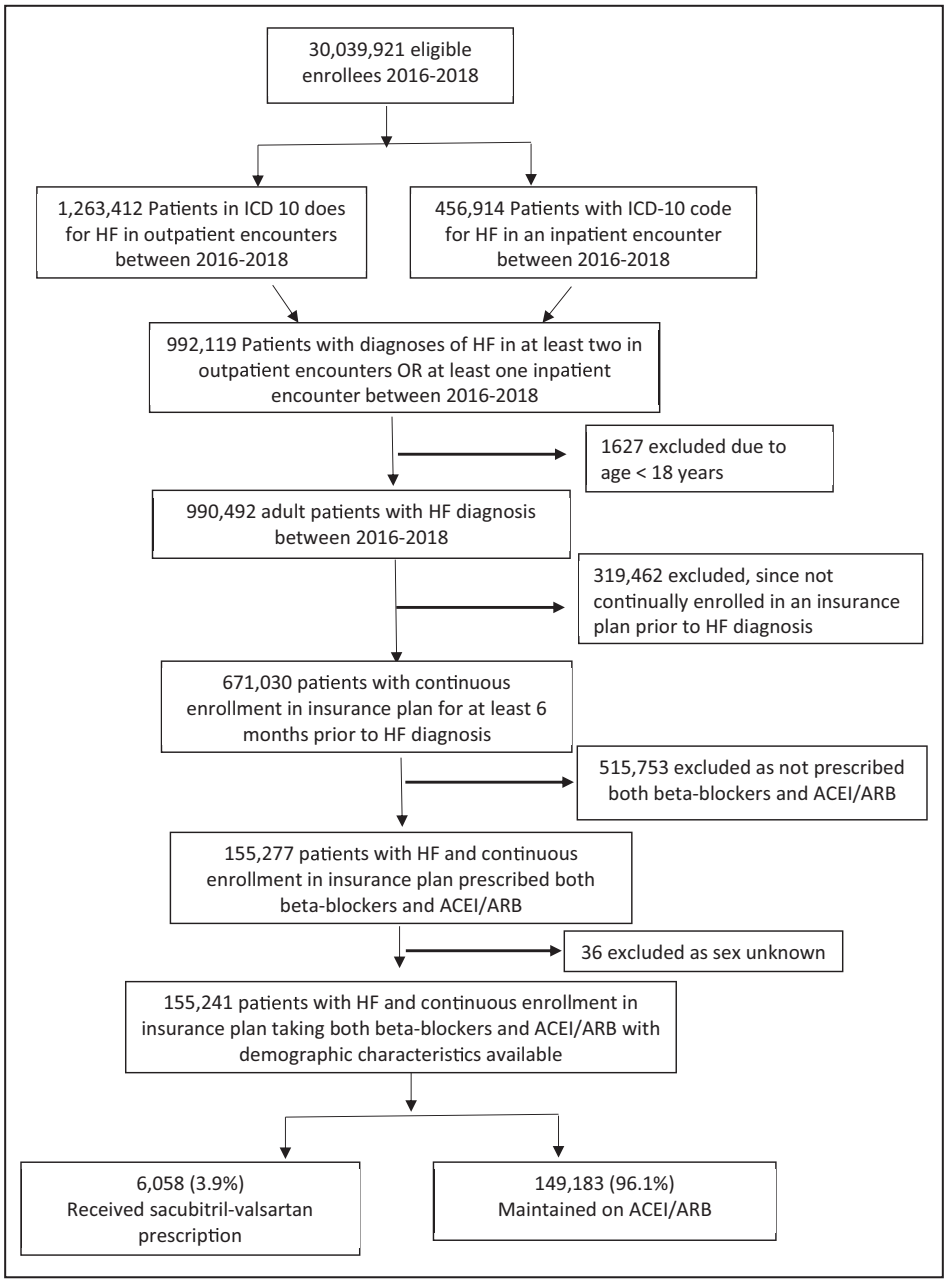

Figure 1. Cohort creation.
ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HF, heart failure; and *ICD-10*, *International Classification of Diseases, Tenth Revision*.

demographics included patient age, sex, race, health plan coverage, and provider specialty at the index date. Race was determined using information obtained by OptumInsight from public records (eg, driver's license data), the first and last name of the beneficiary, and the census block of residence. Provider specialty was determined by identifying the physician prescribing sacubitril-valsartan or ACE inhibitors/ARBs. Comorbidities were identified using previously validated *ICD-10* codes in any position in the 1 year before the index date (Table S1) to maximize capturing all comorbidities. Use of other HF medications was assessed in the 6 months before index date based on pharmacy claims. To examine geographic variation in cost, states were grouped into divisions based on the 2010 US Census data.[13]

Outcome Measures

Outcomes of interest included receipt of sacubitril-valsartan and total OOP cost for the medication per month. We used pharmacy claims and associated

member enrollment data to assess the total OOP cost using deductibles, coinsurances, and copayments associated with sacubitril-valsartan prescription refills. To account for differences in OOP cost related to medication days supplied, we standardized the days supplied for all scripts to 30 days. Specifically, monthly OOP cost was calculated using the sum of copayments and deductibles of prescriptions for an individual, divided by the quantity, and then multiplied by 60 (given the twice daily use of the drug), as summarized below:

$$\text{monthly OOP cost} = 60 \times \left[(\text{copay} + \text{deductible} + \text{coinsurance})/\text{quantity}\right].$$

Statistical Analysis

Comparison of patient characteristics was made between patients with HFrEF who were prescribed sacubitril-valsartan versus ACE inhibitors/ARBs. For categorical variables, we used χ^2 test; and for normally distributed continuous variables, we used independent-sample *t* tests. Next, to identify factors associated with receiving sacubitril-valsartan, we used a multivariable logistic regression model, fitted with patient demographics, clinical characteristics, and the prescribing physician's specialty. These variables were selected on the basis of clinical rationale. We adjusted the logistic coefficients to provide a relative risk (RR) ratio instead of odds ratio to allow for probability interpretation.

OOP cost for sacubitril-valsartan was calculated from the pharmacy claims data, as described above. For mean costs to be comparable across the study years, we inflation adjusted and accounted for case-mix differences over time. All costs were inflation adjusted to 2018 dollars using a proprietary cost factor multiplier table that is provided by OptumInsight. The cost factor multipliers are patient setting–specific multipliers.

We used multilevel generalized linear models using PROC GLIMMIX in statistical analysis system using a log-link and γ distribution to evaluate the association between OOP cost using plan types and patient, provider, and prescription characteristics, with a repeated-measures design for multiple prescriptions per individual. Explanatory variables included age, sex, race, region, type of insurance plan, total number of medications prescribed, Elixhauser comorbidity index before taking sacubitril-valsartan, refill status (first prescription versus refill), and prescribing provider. We imposed $0.01 floor of OOP cost to handle 0 expenditures (14.1% of the sample) in the model. Because patients with multiple refills are more likely to reach their total OOP maximum, which would lead to lower adjusted mean OOP costs per 30-day refill, we performed a sensitivity analysis using a sample of first prescription of sacubitril-valsartan per patient during 2016 to 2018.

To examine whether adjusted OOP costs varied by patients' demographic factors and geographic regions at the population level, we conducted postestimation using the PROC PLM procedure in statistical analysis system conducting least square means using the aforementioned generalized linear mixed models. Calculation of these OOP computes and compares the predicted population marginal means of the fixed effects for each of the covariates in the multivariable model.

All analyses were conducted using Statistical Analysis System Version 9.4 (SAS Institute, Cary, NC). PROC GLIMMIX was used for cost analysis, and the results were stored to apply PROC PLM for generating marginal means of the main factors.

RESULTS

Baseline Characteristics

A total of 70 245 patients with HFrEF were enrolled in our study. Sacubitril-valsartan was prescribed for 5217 (7.4%) patients. Before release of American College of Cardiology/American Heart Association guidelines in May 2017 that endorsed ARNI over ACE inhibitors/ARBs in patients with HFrEF, 3.6% patients in our cohort were prescribed ARNI. After release of guidelines, there was a statistically significant increase in ARNI prescription, with 8.1% patients receiving the medication ($P<0.001$). Among those excluded because of lack of codes specific for HFrEF or because of lack of prescriptions for ACE inhibitors/ARBs and β-blockers, de novo use of sacubitril-valsartan was noted in 1553 patients (0.3% of excluded patients). To increase specificity of our analyses and because of the small number of patients initiated de novo on ARNI, we did not include these in our subsequent analyses.

Table 1 summarizes baseline characteristics of the study cohort, stratified by receipt of sacubitril-valsartan versus ACE inhibitors/ARBs. Compared with patients prescribed ACE inhibitors/ARBs, those receiving sacubitril-valsartan were younger (mean age, 69 versus 73 years) and were more likely to be men (69% versus 59%), Black, Asian, and other race (39.8% versus 37.1%), and commercially insured (22% versus 17%). Patients prescribed sacubitril-valsartan also had a higher burden of comorbidities, including obesity (45% versus 40%), coronary artery disease (89% versus 83%), and ventricular tachycardia (38% versus 20%). Patients receiving sacubitril-valsartan were also more likely to receive prescriptions for aldosterone antagonist (60% versus 32%), diuretics (86% versus 78%), and antiarrhythmics (31% versus 21%). Overall distribution of comorbidity was high in patients prescribed sacubitril-valsartan (comorbidity

Table 1. Baseline Characteristics of Cohort, Stratified by Receipt of Sacubitril-Valsartan

Variable	Sacubitril-valsartan (n=5217)	Angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker (n=65 028)	*P* value
Demographic characteristics			
Age, mean±SD, y	69.4±11.1	73.3±10.8	<0.0001
Male sex, n (%)	3607 (69.1)	38 390 (59.0)	<0.0001
Race or ethnicity, n (%)			<0.0001
White	3140 (60.2)	40 904 (62.9)	
Black	862 (16.5)	9560 (14.7)	
Other*	704 (13.5)	7585 (11.7)	
Unknown/missing	511 (9.8)	6979 (10.7)	
Insurance type, n (%)			<0.0001
Commercial	1136 (21.8)	10 038 (16.7)	
Medicare Advantage	4081 (78.2)	54 990 (84.6)	
Insurance market plan, n (%)			<0.0001
Health maintenance organization	1281 (24.6)	21 693 (33.4)	
Point of service	766 (14.7)	6274 (9.6)	
Other plan†	3170 (60.8)	37 061 (57.0)	
Geographic region, n (%)			<0.0001
New England	132 (2.5)	2069 (3.2)	
Middle Atlantic	541 (10.4)	5435 (8.4)	
East North-Central	369 (7.1)	6763 (10.4)	
West North-Central	620 (11.9)	8491 (13.1)	
South Atlantic	1662 (31.9)	15 420 (23.7)	
East South-Central	268 (5.1)	2555 (3.9)	
West South-Central	715 (13.7)	9392 (14.4)	
Mountain	361 (6.9)	5365 (8.3)	
Pacific	538 (10.3)	9360 (14.4)	
Unknown or Puerto Rico	11 (0.2)	178 (0.3)	
Clinical characteristics, n (%)			
Obesity	2352 (45.1)	25 910 (39.8)	<0.0001
Diabetes	3275 (62.8)	39 465 (60.7)	0.003
Hypertension	5110 (97.9)	63 852 (98.2)	0.21
Chronic kidney disease	3275 (62.8)	39 475 (60.7)	<0.01
Chronic lung disease	2765 (53.0)	34 436 (53.0)	0.95
Coronary artery disease	4622 (88.6)	53 714 (82.6)	<0.0001
Atrial fibrillation	3043 (58.3)	36 396 (56.0)	0.001
Ventricular tachycardia	2004 (38.4)	13 298 (20.4)	<0.0001
Ventricular fibrillation	395 (7.6)	2495 (3.8)	<0.0001
Prescribing physician specialty, n (%)			
Cardiologist	2495 (47.8)	22 380 (34.4)	<0.0001
Other	2722 (52.2)	42 648 (65.6)	
Other medication use, n (%)			
Aldosterone antagonist	3135 (60.1)	20 897 (32.1)	<0.0001
Diuretics	4506 (86.4)	50 629 (77.9)	<0.001
Antiarrhythmics	1600 (30.7)	13 566 (20.9)	<0.0001

*Other represents Asian race and Hispanic ethnicity.
†Other plan represents insurance plan preferred provider organization, exclusive provider organization, indemnity, and other among commercial insurance.

index of 0–7 in 19%, comorbidity index of 8–10 in 29%, comorbidity index of 11–13 in 28%, and comorbidity index of ≥14 in 24%).

Factors Associated With Prescription of Sacubitril-Valsartan

Figure 2 shows results of our multivariable analysis examining factors significantly associated with prescription of sacubitril-valsartan. Demographic characteristics associated with receiving a prescription for sacubitril-valsartan following multivariable adjustment for patient and provider characteristics included age <65 years (RR, 1.45 [95% CI, 1.35–1.56]), male sex (RR, 1.33 [95% CI, 1.26–1.1]), Black, Asian, and other race or ethnicity, including Black race (RR, 1.21 [95% CI, 1.12–1.30]) and Hispanic ethnicity (RR, 1.28 [95% CI, 1.17–1.39]). Other clinical factors significantly associated with prescription for sacubitril-valsartan included presence of coronary artery disease (RR, 1.56 [95% CI, 1. 44–1.69]), atrial fibrillation (RR, 1.16 [95% CI, 1.10–1.24]), obesity (RR, 1.15 [95% CI, 1.08–1.21]), and chronic lung disease (RR, 1.06 [95% CI, 1.00–1.12]). In addition, patients were more likely to be prescribed sacubitril-valsartan when care involved a cardiologist compared with care provided by primary care physician alone (RR, 1.55 [95% CI, 1.46–1.62]). Chronic kidney disease was less likely to be associated with a prescription for sacubitril-valsartan (RR, 0.92 [95% CI, 0.87–0.97]).

OOP Cost and Its Predictors

Commercial Insurance

The mean monthly OOP cost for sacubitril-valsartan among commercially insured patients was $69 (95% CI, $67.7–$70.3; median, $68 [interquartile range, $53–$83]). A large proportion of this OOP cost for sacubitril-valsartan was attributable to copay (mean copay, $52; median, $50). In comparison, mean monthly OOP cost for ACE inhibitors/ARBs was $6.74 (95% CI, $6.71–$6.77; median, $5.24 [interquartile range, $1.30–$10.08]).

Unadjusted mean monthly OOP cost showed significant geographic variation across different US states (Figure 3A). Following multivariable adjustment, the geographic variation in mean monthly OOP cost for sacubitril-valsartan persisted (Table 2). Compared with patients residing in New England region, OOP costs were lower in West North-Central, Pacific, Middle Atlantic, and West South-Central regions, holding other factors constant. Other factors associated with lower mean monthly OOP cost for sacubitril-valsartan for commercially insured patients included a health maintenance organizational (HMO) plan, age <65 years, and greater comorbidity burden while holding other factors constant. OOP cost was also lower in 2016 compared with 2017 and 2018.

Table 3 shows the predicted population mean OOP cost for sacubitril-valsartan. Among patients with commercial insurance, at a population level, demographic factors were not significantly different. However, OOP cost in 2016 was lower compared with 2017 and 2018 for commercially insured patients, increasing from $36 to $60 during this time period, whereas OOP cost remained stable for Medicare Advantage patients. This increase in OOP cost was attributable to increase in copay for commercially insured patients. Regional variation in OOP costs was less extensive and only limited to lower cost in the Pacific region compared with New England. Results of our sensitivity analysis looking at population predicted mean monthly OOP cost using only first prescription fills were similar, with the only variable associated with significant OOP cost difference being year of prescription (lower cost in 2016 compared with 2017 or 2018).

Medicare Advantage

For patients with Medicare Advantage, mean monthly OOP cost for sacubitril-valsartan was $62 (95% CI, $61.4–$62.6; median, $60 [interquartile range, $48–$74]). A large proportion of this OOP cost for sacubitril-valsartan was attributable to copay (mean, $55; median, $42). Mean monthly OOP cost for ACE inhibitors/ARBs was $2.52 (95% CI, $2.51–$2.53; median, $2.00 [interquartile range, $0.31–$2.40]).

Similar to patients with commercial insurance, we observed a statistically significant geographic variation in unadjusted mean monthly OOP cost across different states (Figure 3B). However, the pattern of regional variation was different from commercially insured patients. Following multivariable adjustment, compared with patients residing in the New England region, mean monthly OOP cost was lower among residents of West North-Central, South Atlantic, and East South-Central regions but higher in residents of Mountain, Pacific, Middle Atlantic, and West South-Central regions (Table 2). Other factors associated with lower mean monthly OOP costs included HMO plan, age <65 years, female sex, Black, Asian, and other race, and a greater comorbidity burden. OOP cost was largely stable during the study period from 2016 to 2018 (Table 2).

Among patients with Medicare Advantage, at a population level, demographic variables associated with a lower cost included female sex, Black, Asian, and other race, and an HMO plan. Widespread regional variation in OOP costs persisted, as shown in Table 3. Results of our sensitivity analysis looking at population predicted mean monthly OOP cost for only first medication fill were similar.

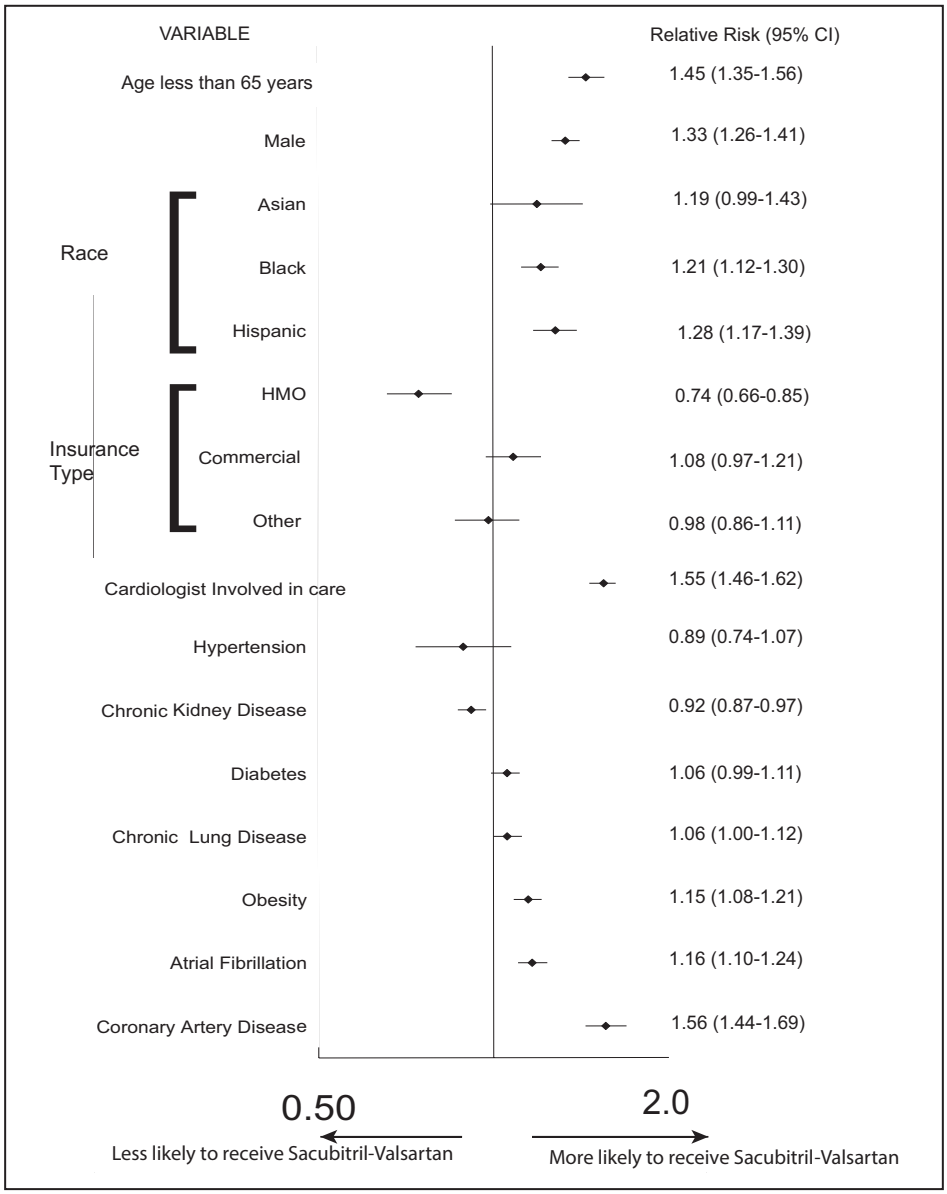

Figure 2. Factors associated with prescription of sacubitril-valsartan.
Primary care provider as reference for cardiologist; White as reference for race (Black, Hispanic ethnicity, and Asian); insurance product point of service as reference for insurance health maintenance organization and other; Medicare Advantage as reference for commercial; and age as reference for ≥65 years. HMO indicates health maintenance organization.

DISCUSSION

The objective of our study was to describe contemporary trends in use of sacubitril-valsartan among patients with HF and identify factors associated with receipt of the medication. We also describe OOP cost associated with use of sacubitril-valsartan and identify factors associated with OOP cost in patients prescribed the medication. We observed that <1 in 10 patients with HFrEF received a prescription for sacubitril-valsartan. Among those prescribed the medication, mean monthly OOP cost was $69 for commercially insured patients and $62 for patients with Medicare Advantage. This is higher than the previously described monthly OOP cost of $57 for sacubitril-valsartan in Medicare beneficiaries with Part D. In contrast, mean monthly OOP cost for ACE inhibitors/ARBs was significantly lower. Furthermore, we observed substantial geographic variation in OOP cost for the medication despite adjusting for several patient- and plan-related characteristics, with a marginal mean monthly OOP cost difference of >$30 across various regions, which was more pronounced among patients with Medicare Advantage. In addition, among those with commercial insurance,

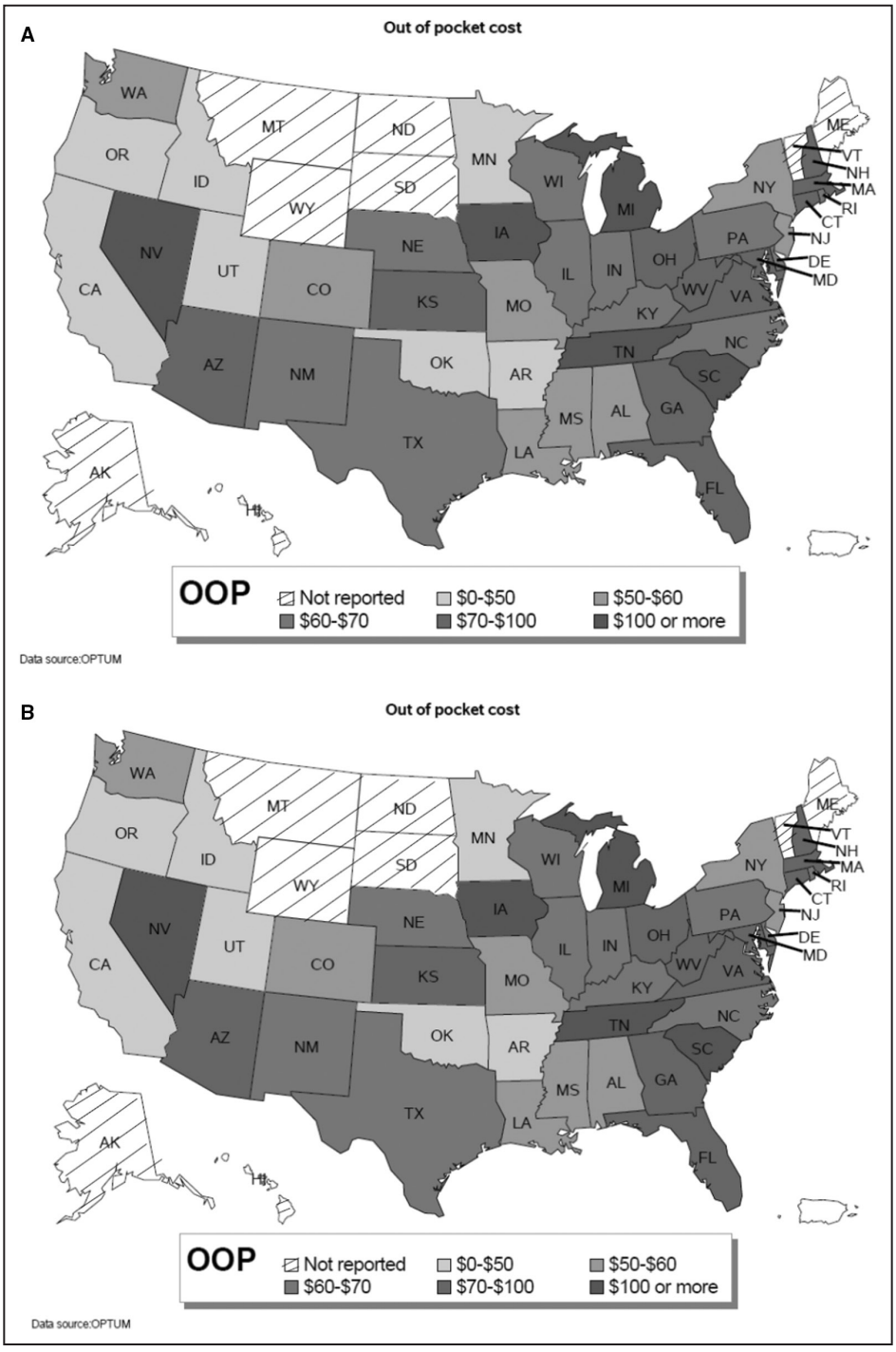

Figure 3. Unadjusted mean monthly out-of-pocket (OOP) cost by state for sacubitril-valsartan for patients with commercial insurance (A) or Medicare Advantage (B).

mean monthly OOP costs increased over time from 2016 to 2018 by ≈$24.

Slow adoption of sacubitril-valsartan has been described previously as well. Two studies assessing prescription of sacubitril-valsartan within the first year of its availability in a large claims data set and a national HF registry showed adoption rates of <3%.[5,6] Our study shows that 3 years after the medication was commercially available, adoption rates remained remarkably low, with only a modest uptick in use since release of major society guidelines in mid-2017 that endorse use of ARNI over ACE inhibitors/ARBs in patients with

Table 2. Factors Associated With Monthly OOP Cost for Sacubitril-Valsartan

Characteristics	Commercial		Medicare advantage	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Insurance plans				
Other	1.20 (1.03–1.40)	0.02	1.48 (1.39–1.59)	<0.0001
POS	1.17 (1.01–1.34)	0.03		
HMO	Reference		Reference	
Age, y				
≥65	1.13 (1.02–1.24)	0.01	1.34 (1.28–1.41)	<0.0001
18–64	Reference		Reference	
Sex				
Women	1.02 (0.93–1.12)	0.51	0.89 (0.86–0.93)	<0.0001
Men	Reference		Reference	
Race or ethnicity				
Asian/Hispanic	0.90 (0.80–1.01)	0.04	0.80 (0.75–0.84)	<0.0001
Black	1.08 (0.97–1.19)	0.68	0.80 (0.76–0.84)	<0.001
White	Reference		Reference	
Comorbidity index				
≥14	0.59 (0.52–0.66)	<0.001	0.86 (0.82–0.91)	<0.0001
11–13	0.67 (0.60–0.75)	<0.001	0.93 (0.88–0.98)	<0.01
8–10	0.89 (0.82–0.97)	0.01	0.99 (0.94–1.05)	0.83
0–7	Reference		Reference	
Year of prescription				
2018	1.66 (1.48–1.86)	<0.001	0.95 (0.90–1.00)	0.06
2017	1.50 (1.33–1.69)	<0.001	0.93 (0.88–0.98)	<0.01
2016	Reference		Reference	
Refill order				
First fill	0.94 (0.86–1.04)	0.26	1.0 (1.01–1.08)	0.01
Refill	Reference		Reference	
Prescribing physician				
Cardiologist	1.04 (0.95–1.13)	0.37	1.05 (1.01–1.09)	<0.01
Noncardiologist	Reference		Reference	
Census division				
West North-Central	0.71 (0.51–0.98)	0.04	0.63 (0.56–0.70)	<0.0001
East North-Central	0.93 (0.67–1.28)	0.64	1.09 (0.97–1.53)	0.16
South Atlantic	0.92 (0.67–1.26)	0.59	0.83 (0.75–0.92)	<0.001
Pacific	0.62 (0.44–0.87)	0.006	1.39 (1.22–1.58)	<0.0001
Mountain	0.74 (0.52–1.05)	0.10	1.40 (1.20–1.55)	<0.0001
East South-Central	0.78 (0.55–1.10)	0.15	0.83 (0.73–0.94)	0.01
Middle Atlantic	0.63 (0.45–0.89)	0.008	1.35 (1.21–1.51)	<0.0001
West South-Central	0.68 (0.49–0.93)	0.02	1.16 (1.02–1.31)	0.02
New England	Reference		Reference	

Generalized linear regression models were used with log-link and γ distribution. All OOP costs were analyzed within the regression, including those with $0 cost sharing. HMO indicates health maintenance organization; OOP, out of pocket; POS, point of service; and RR, relative risk.

HFrEF. This is despite clinical evidence from the largest randomized trial of patients with HFrEF to date, which showed an absolute risk reduction of 3% in all-cause mortality and a 3% absolute risk reduction in HF hospitalization among patients receiving sacubitril-valsartan as opposed to an ACE inhibitor.[2] Although some criticisms of the trial and its methods have been made, evidence remains in favor of sacubitril-valsartan, and it is currently a class I recommendation in all major society guidelines.[3,4]

In our study, factors associated with lower odds for receiving sacubitril-valsartan included presence of an HMO plan and presence of chronic kidney disease. Use of generic and cheaper medications is more common

Table 3. Marginal Mean Monthly OOP Cost for Sacubitril-Valsartan After Multivariable Adjustment

Variable	Commercial insurance, $	Medicare advantage, $
Insurance plan		
Health maintenance organization	43.7 (37.0–51.7)	41.9 (39.2–44.7)
Point of service	51.0 (45.2–57.6)	…
Other plans	52.6 (46.3–59.8)	62.2 (59.0–65.6)
Sex		
Women	49.5 (43.2–56.6)	48.3 (45.7–51.0)
Men	48.5 (43.1–54.6)	54.0 (51.3–56.8)
Race or ethnicity		
White	56.1 (50.0–63.1)	55.0 (52.3–57.8)
Black	57.4 (49.6–66.5)	43.9 (41.2–46.7)
Asian or Hispanic	48.3 (40.7–57.4)	43.8 (41.0–46.8)
Comorbidity index		
≤7	62.7 (54.6–72.0)	54.0 (50.7–57.5)
8–10	57.1 (50.1–65.1)	53.7 (50.7–56.9)
11–13	43.1 (37.4–49.7)	50.0 (47.3–52.9)
≥14	37.2 (32.2–43.0)	46.7 (44.1–49.5)
Year		
2016	36.1 (31.2–41.9)	53.2 (49.9–56.9)
2017	54.2 (47.7–61.5)	49.3 (46.8–52.0)
2018	60.0 (53.0–67.8)	50.6 (48.1–53.3)
Prescription order		
First refill	47.6 (41.5–54.6)	52.2 (49.5–55.1)
Not	50.4 (44.8–56.6)	49.9 (47.4–52.5)
Prescribing physician		
Cardiologist	49.9 (44.3–56.2)	52.3 (49.7–55.0)
Primary care or other	48.0 (42.1–54.8)	49.9 (47.2–52.6)
Census division		
New England	62.7 (45.6–86.2)	49.1 (44.1–54.6)
Pacific	38.7 (32.9–45.6)	68.4 (64.0–73.2)
Middle Atlantic	39.5 (32.8–47.6)	66.4 (62.2–70.8)
East North-Central	58.1 (50.2–67.3)	53.5 (49.5–57.8)
West North-Central	44.4 (38.7–51.0)	30.9 (29.1–32.9)
South Atlantic	57.5 (52.0–63.7)	40.8 (37.3–44.6)
East South-Central	48.8 (41.0–58.2)	40.8 (37.3–44.6)
West South-Central	42.5 (37.7–47.9)	56.9 (53.7–60.3)
Mountain	46.4 (38.2–56.5)	66.9 (62.1–72.0)

OOP indicates out of pocket.

in HMO plans, with in-network physicians being more cost sensitive and preferentially prescribing lower-cost, generic medications. Although sacubitril-valsartan is also beneficial in patients with HFrEF and chronic kidney disease, underuse of angiotensin antagonists in this population has been extensively described. We also noted Black, Asian, and other races having a higher odds of receiving ARNI prescription. This is in contradiction to other studies that identify to patients from ethnic and racial minority groups at risk for not receiving appropriate medical therapy for HFrEF and is likely attributable to differences in our study cohort that comprises all patients who had private insurance. It may reflect differences in insurance plans for White versus Black, Asian, and other individuals as a greater proportion of Black, Asian, and other patients had Medicare Advantage. Clinical factors associated with increased odds for sacubitril-valsartan prescription also included presence of higher comorbidity burden, such as atrial fibrillation, obesity, older age, and coronary artery disease. Notably, the only modifiable factor associated with prescription of sacubitril-valsartan was involvement of a cardiologist compared with a primary care physician in the management of HF. This could reflect a lack of familiarity with the medication among noncardiologists, the fact that primary care physicians are burdened with caring for multiple other comorbidities, or the fact that sicker patients with HFrEF are seen by cardiologists. Nonetheless, benefits with ARNI in HFrEF extend to patients across the wide spectrum of New York Heart Association class II to IV symptoms and should not be withheld in patients with fewer symptoms. These findings suggest that an important driver of getting appropriate guideline-directed medical therapy is a clinician understanding the importance of optimal medical therapy in HFrEF.

Cost remains a major barrier in easy accessibility to sacubitril-valsartan. In comparison to ACE inhibitors/ARBs, where mean monthly OOP cost was $3.34 in our cohort, OOP costs for sacubitril-valsartan among those prescribed this medication remain substantially higher. Sociodemographic factors associated with higher monthly OOP cost in our study included factors associated with worse HF severity and higher risk for mortality and rehospitalizations, such as age >65 years and higher comorbidity burden.[14,15] Although we did note that the monthly OOP cost decreased for patients with increasing comorbidities, this is likely attributable to such patients meeting their deductibles and not attributable to lower drug price for these individuals. We also observed substantial geographic variation in the marginal mean monthly OOP cost for the medication by >40% across different regions, more extensively among individuals with Medicare Advantage. Observed cost variations across different regions varied differently for patients with commercial insurance compared with those with Medicare Advantage. Monthly OOP cost also increased from 2016 to 2018 among individuals with commercial insurance. Notably, in our study, we did not have data from drug assistance programs sponsored by the manufacturer that may help patients with commercial insurance meeting certain criteria obtain sacubitril-valsartan at a lower price. However, a previous study looking at temporal trends in OOP costs for the most prescribed brand-name drugs in the United States shows a similar steady increase in cost

between 2012 and 2017, with nearly all drugs showing an increase in cost every year.[16] This increase in price was also noted for drugs with other equivalent branded or generic options. Our study mimics these findings.

Data behind how drug prices are set by manufacturers are vague and difficult to comprehend. Drug pricing can be set by the manufacturer independently at any time for a wide range of reasons, which has led to allegations of price gouging.[17] At other times, drug manufacturers set drug pricing based after negotiations with a pharmacy benefits manager who represents the insurance company. Drug manufacturers often offer rebates on the drug prices to insurance companies so that they are the preferred medication on a plan. Increasing data now suggest an increase in rebates leads to increased OOP costs for patients, and the US Department of Health and Human Services recently concluded that existing rebate systems harm both federal health care programs as well as their beneficiaries.[18] Although the exact reason for geographic variation and temporal increase in pricing for ARNI cannot be determined from our study, we suspect these factors play a role.

Our results highlight the variable and complex nature of drug pricing and are concerning given prior studies suggesting that most Americans lack understanding of cost sharing associated with medical care. In a study by Loewenstein et al, only 14% of enrollees in employee-sponsored health insurance plans provided correct answers related to deductibles, copayments, and OOP maximums.[19] Furthermore, it also highlights the important role health care providers can play in educating patients about resources available to explore drug pricing through websites given extreme variability in pricing. Moreover, health care providers should also consider risk-benefit discussions when it comes to nongeneric medications, such as sacubitril-valsartan, when there exists a substantially cheaper and slightly less efficacious option in the form of ACE inhibitors and ARBs for chronic disease conditions as these high OOP costs are recurring. Yet, existing literature suggests that cost discussions are rarely brought up by treating physicians.[20] An important contributing reason includes lack of physician awareness about prescription prices at the time of clinical encounter, with patients being made aware of drug prices at pharmacies. Accordingly, increasing price transparencies at the time of clinical encounter may help facilitate appropriate communication about drug prices with patients.

The findings of our study should be in interpreted in the light of several considerations. First, this is a retrospective observational study. Although we had numerous factors we could account for in multivariable analyses, some of our findings may be explained by residual confounding by factors we were unable to include, such as access to care or New York Heart Association class. Regardless, the broad nature of this database describes real-world adoption and pricing for sacubitril-valsartan in a large cohort with relevance for current practice. Second, we relied on billing codes in identifying our cohort of patients with HFrEF, and this may not fully capture the population with HFrEF that sacubitril-valsartan is most relevant for. However, we conservatively restricted our cohort to patients on prior ACE inhibitors/ARBs and β blockers to identify ideal candidates for sacubitril-valsartan to limit the potential for this bias. Our findings may even underestimate the potential lower use of this therapy. Third, we were unable to account for certain characteristics while examining factors associated with OOP cost, such as patient income or household wealth. Such factors are also likely to explain the ability of patients to use these new agents and could exacerbate existing differences across sex and race. Fourth, we do not have data from drug assistance programs sponsored by the manufacturer that may help patients meeting certain criteria obtain sacubitril-valsartan at a lower price.

CONCLUSIONS

In our study from a large insurance claims data set, adoption of sacubitril-valsartan in patients with HFrEF remains low. The only modifiable factor associated with prescription of sacubitril-valsartan was provision of care by a cardiologist. Furthermore, mean monthly OOP cost for the medication remains high, with substantial geographic variation in its pricing.

ARTICLE INFORMATION

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Supplemental Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. ICD 10 codes used

Condition	ICD 10 codes
Heart Failure with Reduced Ejection Fraction	I150.2
Obesity	E66.x
Diabetes	E10.0 - E10.9, E11.0-E11.9, E12.0 - E12.9, E13.0 -E13.9, E14.0 - E14.9
Hypertension	I10.x, I11.x-I13.x, I15.x
Chronic Kidney Disease	I12.0, I13.1, N18.x, N19.x, N25.0, Z49.0 - Z49.2, Z94.0, Z99.2
Chronic Lung Disease	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3
Coronary Artery Disease	DX I20.0, I20.1, I20.8, I20.9, I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I21.9, I21.A1, I21.A9, I22.0, I22.1, I22.2, I22.8, I22.9, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.7, I23.8, I24.0, I24.1, I24.8, I24.9, I25.10, I25.110, I25.111, I25.118, I25.119, I25.2, I25.3, I25.41, I25.42, I25.5, I25.6, I25.700, I25.701, I25.708, I25.709, I25.710, I25.711, I25.718, I25.719, I25.720, I25.721, I25.728, I25.729, I25.730, I25.731, I25.738, I25.739, I25.750, I25.751, I25.758, I25.759, I25.760, I25.761, I25.768, I25.769, I25.790, I25.791, I25.798, I25.799, I25.810, I25.811, I25.812, I25.82, I25.83, I25.84, I25.89, I25.9
Atrial Fibrillation	I48.0, I48.1, I48.2, I48.91
Ventricular Tachycardia	I47.2
Ventricular Fibrillation	I49.01