

Variation in Early Diffusion of Sacubitril/Valsartan and Implications for Understanding Novel Drug Diffusion

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Sacubitril/valsartan was approved by the FDA on July 7, 2015, for the treatment of heart failure with reduced ejection fraction (HFrEF).¹ In the PARADIGM-HF study, sacubitril/valsartan demonstrated a 21% relative reduction in hospitalizations for HFrEF and a 26% relative decrease in mortality compared with standard angiotensin-converting enzyme (ACE) inhibitor therapy.² Despite this and a class I indication from the American Heart Association, the American College of Cardiology, and the Heart Failure Society of America,³ early reports have found lower-than-anticipated rates of early adoption,⁴ prompting much discussion in both cardiology and health policy circles. To date, only high out-of-pocket drug costs have been identified as a barrier to early drug diffusion.⁵⁻⁷

Based on work from other fields, we know that patient, provider, and practice characteristics can also affect early drug diffusion. For example, a recent study of the diffusion of new, similarly expensive antidiabetic drugs found that most early use was driven by a small group of “high prescribers” operating in specific practice settings.⁸ Variation in the use of sacubitril/valsartan for HFrEF and factors associated with early diffusion are less well understood. Because 80% of deaths from heart failure occur in individuals 65 years and older,⁹ the aim of this study is to explore the variation in the use of sacubitril/valsartan in eligible Medicare beneficiaries with HFrEF between 2016 and 2018, after controlling for out-of-pocket co-payments.

METHODS

This study was approved by the institutional review board at Dartmouth College. This study is also compliant with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for retrospective cohort studies.

Study Population

We used the complete 100% national sample of fee-for-service (FFS) patients insured by Medicare in 2016 to 2018. We first identified Medicare beneficiaries who were 65 years or older on January 1 of each year and had 12 months of continuous parts A and B coverage from

ABSTRACT

OBJECTIVES: In the PARADIGM-HF trial, sacubitril/valsartan demonstrated a 20% reduction in mortality and heart failure hospitalization compared with standard angiotensin-converting enzyme inhibitor therapy. Despite this and a class I indication, drug diffusion has been much slower than anticipated. This study aims to examine the variation in early diffusion of sacubitril/valsartan and describe the factors associated with high and low rates of early use.

STUDY DESIGN: Annual, cross-sectional analyses between January 2016 and December 2018.

METHODS: We created a nationally representative cohort of Medicare fee-for-service beneficiaries with heart failure with reduced ejection fraction fully enrolled in parts A, B, and D for at least 1 year between 2016 and 2018. Sacubitril/valsartan use was determined using National Drug Codes. We generated age, sex, and race-adjusted rates of sacubitril/valsartan prescribing by hospital referral region from 2016 to 2018. We also examined the factors associated with high and low rates of early use.

RESULTS: Early use rates of sacubitril/valsartan were low: 1.9% in 2016, 3.3% in 2017, and 4.0% in 2018. Even after controlling for out-of-pocket co-payments, there was substantial geographic variation in early use, with most early use concentrated in the Northeast and South.

CONCLUSIONS: There has been substantial variation in the early diffusion of sacubitril/valsartan. In addition to drug cost, geographic prescribing patterns appear to play a major role in early drug diffusion.

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the respective Medicare Beneficiary Summary File. We then searched their inpatient (Medicare Provider Analysis and Review [MedPAR]) and outpatient (Physician/Supplier Part B file and Outpatient file) claim records to identify diagnoses of HFREF using the *International Classification of Diseases, Tenth Revision* codes I50.2x and I50.4x. Patients with at least 1 inpatient claim or at least 2 outpatient claims with these codes, at least 7 days apart in a given calendar year, were determined to have HFREF. The date of the inpatient hospitalization or the date of the first HFREF diagnosis was considered the index HFREF date.

To determine comorbidities and health care utilization in the year prior, we then limited the study population to beneficiaries with at least 1 year of FFS coverage prior to their index HFREF date. We determined sociodemographic characteristics including age, sex, race, dual Medicare/Medicaid eligibility, geographic region,^{10,11} and zip code tabulation area–level estimates of socioeconomic status¹² using the Medicare Master Beneficiary Summary File. We determined HF severity using the MedPAR file and comorbidities using the Chronic Conditions Data Warehouse.¹³ Finally, to examine drug use, we limited the study population to patients who were fully enrolled in Part D for at least 1 year after their HFREF index date.

Sacubitril/Valsartan Exposure

Sacubitril/valsartan use was determined using National Drug Codes (**eAppendix A** [eAppendices available at ajmc.com]). Any beneficiary with at least 1 fill for sacubitril/valsartan in the calendar year was included. All others were considered eligible but not initiated on sacubitril/valsartan therapy. We report age, sex, and race (ASR)–adjusted rates of sacubitril/valsartan use by hospital referral region (HRR).

For all beneficiaries who received sacubitril/valsartan, we used Medicare Part D to determine out-of-pocket co-payments. The amount paid out of pocket by the beneficiary is determined by Medicare based on the 2018 4-phase Part D plan, which includes (1) an initial \$405 deductible, (2) a standard coverage period until total drug costs reach \$3750, (3) a coverage gap with 35% brand-name and 44% generic cost sharing until out-of-pocket costs reach \$5000, and (4) catastrophic coverage with 5% cost sharing thereafter.^{14,15} Because Part D considers all other drug costs that contribute toward a patient's deductible, the out-of-pocket cost per fill is an accurate reflection of what each beneficiary pays for sacubitril/valsartan. We standardized fill costs to 30 days for ease of comparison.

Statistical Analyses

We generated ASR-adjusted rates of sacubitril/valsartan prescribing by HRR in each year between 2016 and 2018 and then pooled across years. We used this to create heat maps of diffusion and to determine high-/low-prescribing HRRs. For the top- and bottom-prescribing HRRs in each year, we determined the mean (SD) out-of-pocket

TAKEAWAY POINTS

There has been substantial variation in the early diffusion of sacubitril/valsartan. Geographic prescribing patterns appear to play a major role in early drug diffusion.

- ▶ Despite the success of sacubitril/valsartan in clinical trials, early diffusion has been slow and highly variable.
- ▶ Even after controlling for drug costs, local prescribing patterns significantly predict early diffusion.
- ▶ For health systems and health plans, local prescribing patterns play a major role in early drug diffusion and can serve as another tool to optimize the speed of diffusion of novel therapies into clinical practice.

beneficiary co-payment per 30-day fill in each year. We then used multivariable logistic regression and a year-region indicator to explore how the impact of geographic region on likelihood of receiving sacubitril/valsartan changed over the 3 years of the study. All analyses were performed between May 2020 and July 2020 using SAS version 9.4 (SAS Institute).

RESULTS

In 2016, we identified 4182 Medicare beneficiaries who received sacubitril/valsartan. In 2017, we identified 7690 beneficiaries who received sacubitril/valsartan (an 83% relative increase from 2016), and by 2018 we identified 9594 beneficiaries who received sacubitril/valsartan (a 25% relative increase from 2017). The mean age of beneficiaries who received sacubitril/valsartan was 76 years, compared with 80 years among those who did not receive sacubitril/valsartan (**Table 1**). Sixty-five percent of beneficiaries who received sacubitril/valsartan were men, compared with 51% of those who did not. Geographically, 23% of all early sacubitril/valsartan use was in the South Atlantic region, followed by the Middle Atlantic region at 17%. More than 66% of sacubitril/valsartan use was in urban areas. Rates of HF hospitalizations in the year prior were similar between beneficiaries who received sacubitril/valsartan and those who did not (18.5% vs 18.9%). Rates of β -blocker use were similar between those who did and did not receive sacubitril/valsartan (69% vs 67%). More than 21% of patients who received sacubitril/valsartan were also receiving a mineralocorticoid receptor antagonist, compared with only 16% of those who did not receive sacubitril/valsartan. Among those who did not receive sacubitril/valsartan, 53% received an ACE inhibitor or angiotensin receptor blocker (ARB). Coronary artery disease was more common among those who received sacubitril/valsartan (91% vs 85%; $P < .001$), whereas chronic kidney disease was less common (66% vs 71%; $P < .001$).

There was substantial geographic variation in the ASR-adjusted rates of sacubitril/valsartan use among eligible beneficiaries with HFREF between 2016 and 2018 (**Figure 1**). In 2016, there were only pockets of high use rates in the Mid-Atlantic and northern Texas/Oklahoma. In 2017, additional areas of high use could be seen in the Southeast and Appalachia. By 2018, use across the Northeast and South was high and the previously seen areas of high use in the

TABLE 1. Characteristics of Beneficiaries Who Received Sacubitril/Valsartan, 2016-2018

	Sacubitril/ valsartan		No sacubitril/ valsartan	
	n or mean	% or SD	n or mean	% or SD
n	21,466	3.09	672,683	96.91
Age in years, mean (SD)	76.17	6.99	79.58	8.11
Female, n (%)	7403	34.49	327,638	48.71
Race, n (%)				
White	18,149	84.55	573,394	85.24
Black	1998	9.31	63,601	9.45
Hispanic	330	1.54	11,191	1.66
Other	989	4.61	24,497	3.64
Dual eligibility, n (%)	4595	21.41	189,180	28.12
% with bachelor's degree, mean (SD)	23.32	14.05	22.64	13.57
% below federal poverty level, mean (SD)	9.54	6.63	9.49	6.45
Geographic region, n (%)				
East South Central (AL, KY, MS, TN)	1771	8.25	49,696	7.39
Middle Atlantic (NJ, NY, PA)	3558	16.58	98,707	14.67
East North Central (WI, MI, IL, IN, OH)	3318	15.46	121,801	18.11
Mountain (MT, ID, WY, NV, UT, CO, AZ, NM)	706	3.29	29,761	4.42
New England (ME, NH, VT, MA, CT, RI)	790	3.68	37,246	5.54
Pacific (WA, OR, CA)	2291	10.67	74,703	11.11
South Atlantic (WV, MD, DE, VA, NC, SC, GA, FL)	4953	23.07	132,069	19.63
West North Central (ND, SD, NE, KS, MN, IA, MO)	1153	5.37	51,177	7.61
West South Central (TX, OK, AR, LA)	2926	13.63	77,523	11.52
Urban/rural, n (%)				
Urban	14,196	66.13	435,414	64.73
Large rural	18,151	42.28	557,808	41.46
Small rural/isolated	1707	3.98	56,901	4.23
HF severity, n (%)				
No HF hospitalizations in year prior	17,496	81.51	545,904	81.15
1-2 HF hospitalizations in year prior	3458	16.11	110,170	16.38
> 2 HF hospitalizations in year prior	512	2.39	16,609	2.47
Concurrent MRA use ^a	4653	21.68	108,598	16.14
Concurrent β-blocker use ^a	14,785	68.88	451,632	67.14
ACE inhibitor/ARB use prior to admission	10,580	49.29	518,040	44.25
ACE inhibitor/ARB use after discharge	-	-	356,521	53.02
≥ 1 fill for sacubitril/valsartan	15,952	74.31	-	-
Comorbidity burden, n (%)				
Coronary artery disease	19,596	91.29	569,083	84.60
Chronic kidney disease	14,082	65.60	478,016	71.06
Diabetes CCW flag	11,587	53.98	354,569	52.71
≥ 5 CCW comorbidity flags	20,160	93.92	640,192	95.17
> 30-day inpatient/postacute care stay in year prior	235	1.09	10,856	1.61

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCW, Chronic Conditions Data Warehouse; HF, heart failure; MRA, mineralocorticoid receptor antagonist.

^aConcurrent use is defined as at least 1 fill in the 90 days prior to index admission and at least 1 fill after hospital discharge.

Southwest, Southeast, and Appalachia spread to surrounding areas, illustrating the slow but steady diffusion.

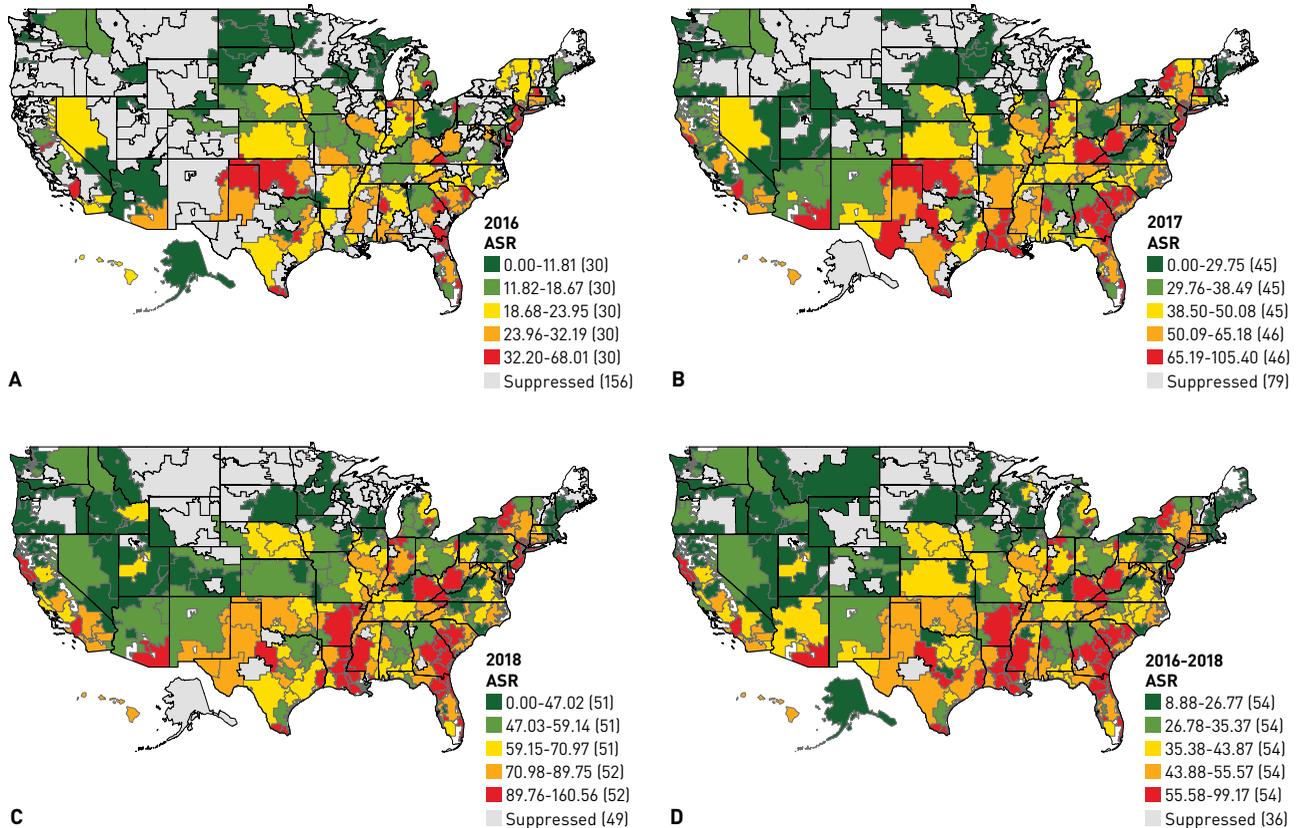
In 2016, the highest ASR-adjusted use rate was in Bryan, Texas (ASR rate, 68.0 per 1000 eligible HFREF beneficiaries) (Figure 2). The mean (SD) out-of-pocket cost per 30-day fill in the top 5 prescribing HRRs was \$56.84 (\$11.27). By comparison, the lowest (nonzero) prescribing HRR was Boston, Massachusetts (ASR rate, 7.9 per 1000 eligible HFREF beneficiaries). The mean (SD) out-of-pocket cost per 30-day fill in the 5 lowest-prescribing HRRs was \$66.02 (\$19.37).

By 2018, the highest-prescribing HRR was Santa Rosa, California (ASR rate, 160.6 per 1000 eligible HFREF beneficiaries, a 135% increase in use compared with the highest-prescribing HRR in 2016). The mean (SD) out-of-pocket cost per 30-day fill in the top 5 prescribing HRRs in 2018 was \$56.57 (\$11.77) (Figure 2). The lowest (nonzero) prescribing HRR was Madison, Wisconsin (ASR rate, 13.7 per 1000 eligible HFREF beneficiaries, a 73% increase in use compared with the lowest-prescribing HRR in 2016). The mean (SD) out-of-pocket cost per 30-day fill in the 5 lowest-prescribing HRRs was \$75.09 (\$14.93).

To examine the diffusion of sacubitril/valsartan over time and the impact of regional practice patterns on drug diffusion, we calculated the odds of receiving sacubitril/valsartan based on year and region in Table 2. Among eligible patients with HFREF, the odds of receiving sacubitril/valsartan increased with each passing year, but the increase from 2016 to 2017 (odds ratio [OR], 1.70 in 2017 vs 2016; 95% CI, 1.64-1.76; *P* < .001) was larger than the increase from 2017 to 2018 (OR, 2.06 in 2018 vs 2016; 95% CI, 1.98-2.14; *P* < .001). Regionally, the lowest-prescribing region was the Midwest and the highest was the Northeast (OR, 1.45 vs Midwest; 95% CI, 1.40-1.50; *P* < .001).

In Table 3, we examine the impact of geographic region, by year, on sacubitril/valsartan diffusion, again after controlling for patient characteristics and out-of-pocket costs. Here we found that initially in 2016, there was no statistically significant difference between the use rate of sacubitril/valsartan in the Midwest (reference region and lowest-prescribing HRR) and the West (OR, 1.11; 95% CI, 1.00-1.22; *P* = .054). In the Northeast and South, use rates of sacubitril/

FIGURE 1. Geographic Variation in Sacubitril/Valsartan Use Among Eligible HF_rEF Beneficiaries, 2016 Through 2018 and Pooled*



ASR, age, sex, and race-adjusted rates of sacubitril/valsartan use by HRR; HF_rEF, heart failure with reduced ejection fraction; HRR, hospital referral region.
 *Panel A shows HRR rates of sacubitril/valsartan use among eligible beneficiaries with HF_rEF in 2016. Panel B shows HRR-level sacubitril/valsartan use among eligible beneficiaries with HF_rEF in 2017. Panel C shows HRR-level sacubitril/valsartan use among eligible beneficiaries with HF_rEF in 2018. Panel D shows HRR-level sacubitril/valsartan use among eligible beneficiaries with HF_rEF pooled between 2016 and 2018.

valsartan were higher (OR, 1.52; 95% CI, 1.40-1.66; $P < .001$ in the Northeast; OR, 1.40; 95% CI, 1.30-1.51; $P < .001$ in the South). Between 2016 and 2017, the rate of sacubitril/valsartan use increased significantly in all regions, but the largest proportional increase was observed in the West (OR, 1.11 in 2016; OR, 2.12 in 2017) such that by the end of 2017, the rates of sacubitril/valsartan use were more similar across the Northeast (OR, 3.18), South (OR, 2.84), and West (OR, 2.58) compared with the rate in the reference region (Midwest 2016).

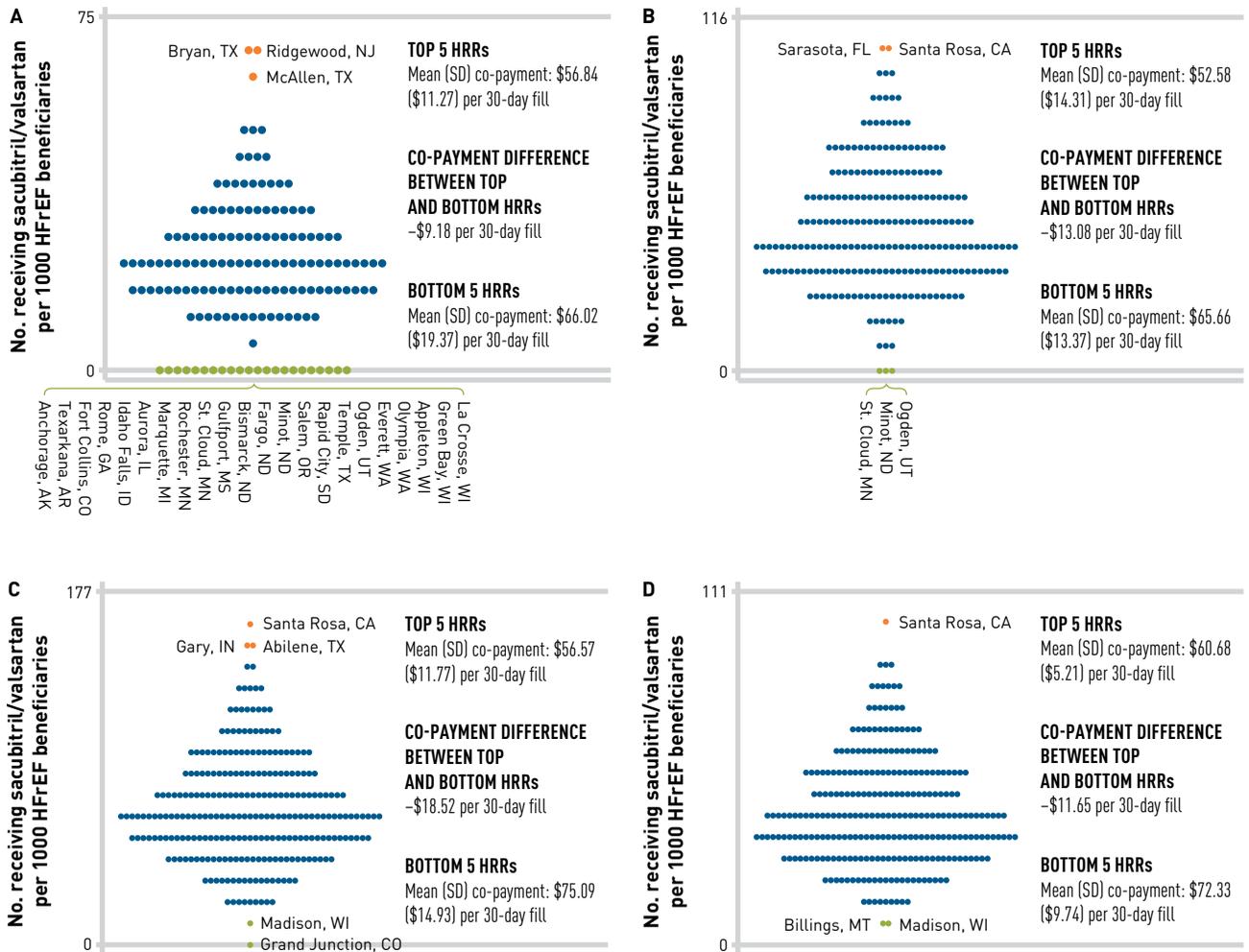
DISCUSSION

We detected significant geographic variation in the diffusion of sacubitril/valsartan since its approval in July 2015. Despite a class I recommendation encouraging providers to initiate it in eligible patients and switch patients already on ACE inhibitors/ARBs to it,³ the early rates of sacubitril/valsartan use among eligible beneficiaries with HF_rEF were low. Although the rate of sacubitril/valsartan use

among eligible beneficiaries with HF_rEF increased 83% between 2016 and 2017, it increased only 25% between 2017 and 2018. Much of this early increase between 2016 and 2017 occurred in the West. Importantly, we found use rates of other guideline-directed medical therapies for HF, such as β -blockers and mineralocorticoid receptor antagonists, and preadmission ACE inhibitor/ARB use and postdischarge ACE inhibitor/ARB use in the non-sacubitril/valsartan group, similar to previously published rates among Medicare beneficiaries.¹⁶⁻¹⁸

On average, beneficiaries who received sacubitril/valsartan were younger and more likely to be male and White. This has been observed previously in work by Sangaralingham et al using commercial claims.¹⁹ This work extends the finding to Medicare beneficiaries with Part D and notes that, on average, those who received sacubitril/valsartan were younger and “healthier” than the average Medicare beneficiary with HF_rEF.²⁰ In addition, this work adds information about geographic prescribing patterns,

FIGURE 2. Age, Sex, and Race-Adjusted Use Rates per 100,000 Beneficiaries With HFREF by HRR, 2016 Through 2018 and Pooled*



HFREF, heart failure with reduced ejection fraction; HRR, hospital referral region.

*Panel A shows the highest and lowest HRR rates of sacubitril/valsartan use among eligible beneficiaries with HFREF in 2016 and the mean co-payments per 30-day fill in the highest and lowest HRRs. Panel B shows the highest and lowest HRR rates of sacubitril/valsartan use among eligible beneficiaries with HFREF in 2017 and the mean co-payments per 30-day fill in the highest and lowest HRRs. Panel C shows the highest and lowest HRR rates of sacubitril/valsartan use among eligible beneficiaries with HFREF in 2018 and the mean co-payments per 30-day fill in the highest and lowest HRRs. Panel D shows the highest and lowest HRR rates of sacubitril/valsartan use among eligible beneficiaries with HFREF pooled across 2016 through 2018 and the mean co-payments per 30-day fill in the highest and lowest HRRs.

finding that early sacubitril/valsartan use was concentrated in the Northeast and South, with areas of high use in Appalachia, Arizona, and the Mid-Atlantic.

Previous work by DeJong et al using Medicare formulary and pricing files to estimate out-of-pocket co-payments suggested that the high out-of-pocket costs, which they estimated to be \$57 per 30-day fill, were likely a significant barrier to sacubitril/valsartan diffusion.^{14,21} In this study, we confirm and extend those findings. By using Part D data to directly measure the out-of-pocket costs per 30-day fill per beneficiary, we are able to calculate a more accurate assessment of out-of-pocket costs. Moreover, we are able to observe

the difference in cost between high- and low-prescribing HRRs (pooled 3-year difference of \$11.65 per 30-day fill) and note that the difference in out-of-pocket costs between high- and low-prescribing HRRs effectively doubled over the 3-year time period (\$9.18 per 30-day fill in 2016 to \$18.52 per 30-day fill in 2018). In addition, having 3 years of cost data allows us to observe that mean out-of-pocket costs in the high-prescribing HRRs did not change (\$56.84 per 30-day fill in 2016 vs \$56.57 per 30-day fill in 2018) but that the mean out-of-pocket costs in the low-prescribing HRRs increased approximately 14% over the same time period (\$66.02 per 30-day fill in 2016 vs \$75.09 per 30-day fill in 2018).

Importantly, however, even after controlling for cost, geographic prescribing patterns remained significantly associated with likelihood of receiving sacubitril/valsartan. Beneficiaries in the Northeast and South were 26% to 45% more likely to receive sacubitril/valsartan than beneficiaries living in the Midwest between 2016 and 2018. We also found that adoption lagged in the West in 2016, but between 2016 and 2017, the rate of increase in the West outpaced all other regions, such that by the end of 2017, the odds of receiving sacubitril/valsartan were much more similar in the Northeast, South, and West. Use rates in the Midwest remained the lowest.

Many possible explanations exist for these significantly different regional trends. First, as the cost/co-payment data from this study and others demonstrate, regions with lower use rates have higher co-payments, and high co-payments are known to be associated with slower drug diffusion.²² However, even after controlling for co-payment, we found significant variation in sacubitril/valsartan use by geographic region. Second, it is possible that the pharmaceutical marketing efforts were more heavily targeted toward one region vs another. For example, after seeing unexpected low use rates in the West in 2016, given the population of eligible beneficiaries in that area, it is possible that enhanced marketing efforts directed at the West explain some of the large increase in sacubitril/valsartan use between 2016 and 2017.

Next, we know from CDC data that the average patient with HFrEF in the Midwest tends to be “healthier,” defined by lower rates of comorbidities, hospitalizations, and HF mortality, compared with other regions.²³ These “healthier” patients might exacerbate provider inertia, making them more reluctant to risk a transition in therapy to a new, but more expensive, drug in a stable patient. We also know from prior work that provider familiarity with a drug is associated with increased use.^{8,24,25} It is therefore possible that more providers in the Northeast and South were exposed to sacubitril/valsartan earlier—perhaps in clinical trials—such that by the time it was FDA approved, they were more comfortable initiating it. Relatedly, prior work examining the diffusion of similarly expensive, novel antidiabetic agents found that much of the early use was driven by a few high-prescribing providers.⁸ Given the overall low rates of use of sacubitril/valsartan, a few aggressive prescribers in a geographic area could increase the overall rate of use in that area and, in doing so, expose their colleagues to the novel therapy, simultaneously decreasing regional provider inertia.

Limitations

The primary limitation of this study is the use of claims data and their lack of clinical granularity. Therefore, we are not able to comment on appropriateness of drug use. Second, this study is limited to FFS Medicare beneficiaries with Part D pharmaceutical coverage. Caution should be used in extrapolating these results to other populations. Third, we do not have access to data regarding the marketing efforts of pharmaceutical companies and where they deployed advertising resources over this time period. Fourth, we have information about only filled prescriptions. We do not know

TABLE 2. Association Among Year, Region, and Use of Sacubitril/Valsartan Among Eligible Medicare Beneficiaries With HFrEF, 2016-2018*

Variable	Odds ratio	Lower 95% CI	Higher 95% CI	P
Year				
2017	1.70	1.64	1.76	<.001
2018	2.06	1.98	2.14	<.001
Geographic region				
Northeast	1.45	1.40	1.50	<.001
South	1.26	1.22	1.30	<.001
West	1.15	1.11	1.20	<.001

HF, heart failure; HFrEF, HF with reduced ejection fraction; HRR, hospital referral region.

*Model is adjusted for age, sex, race, dual eligibility, urban/rural area, zip code tabulation area-level percent poverty, number of HF hospitalizations in the year prior, concurrent β-blocker use, concurrent mineralocorticoid receptor antagonist use, coronary artery disease, chronic kidney disease, diabetes, at least 5 chronic comorbidities, and HRR-level average sacubitril/valsartan co-payment.

For year, the reference is 2016 because this year had the lowest age, sex, and race-adjusted HRR-level rate of sacubitril/valsartan use among eligible beneficiaries with HFrEF.

For geographic region, the reference is Midwest because this region had the lowest age, sex, and race-adjusted HRR-level rate of sacubitril/valsartan use among eligible beneficiaries with HFrEF.

TABLE 3. Association Between the Interaction of Year and Region With the Use of Sacubitril/Valsartan Among Eligible Medicare Beneficiaries With HFrEF, 2016-2018

Region*year interaction	Odds ratio	Lower 95% CI	Higher 95% CI	P
Midwest in 2017	1.78	1.65	1.92	<.001
Midwest in 2018	2.26	2.10	2.44	<.001
Northeast in 2016	1.52	1.40	1.66	<.001
Northeast in 2017	2.68	2.48	2.89	<.001
Northeast in 2018	3.18	2.95	3.43	<.001
South in 2016	1.40	1.30	1.51	<.001
South in 2017	2.25	2.10	2.42	<.001
South in 2018	2.84	2.64	3.10	<.001
West in 2016	1.11	1.00	1.22	.054
West in 2017	2.12	1.96	2.30	<.001
West in 2018	2.58	2.39	2.79	<.001

HF, heart failure; HFrEF, HF with reduced ejection fraction; HRR, hospital referral region.

*Model is adjusted for age, sex, race, dual eligibility, urban/rural area, zip code tabulation area-level percent poverty, number of HF hospitalizations in the year prior, concurrent β-blocker use, concurrent mineralocorticoid receptor antagonist use, coronary artery disease, chronic kidney disease, diabetes, at least 5 chronic comorbidities, and HRR-level average sacubitril/valsartan co-payment.

For all interactions, the comparison is the Midwest region in 2016 because this region*year had the lowest age, sex, and race-adjusted HRR-level rate of sacubitril/valsartan use among eligible beneficiaries with HFrEF.

how many prescriptions were written for sacubitril/valsartan and never filled due to cost or other prohibitive factors. Although we expect that reasons for not filling a new prescription for sacubitril/valsartan should be randomly distributed, if a specific reason was more common in a given area, this could introduce bias. Because approximately 25% of patients who received sacubitril/valsartan only had 1 fill, we compared baseline characteristics between beneficiaries who received only 1 fill and more than 1 fill and found that there are clinically significant differences (eAppendix B). Finally, clinical contraindications to sacubitril/valsartan are poorly coded in claims data. Therefore, we were unable to exclude these patients. This may cause the rate of uptake to appear lower than expected, but because only a small number of individuals have true clinical contraindications to sacubitril/valsartan and/or ACE inhibitors/ARBs, we would not expect this to alter the study's findings.

CONCLUSIONS

Between 2016 and 2018, the overall rate of sacubitril/valsartan use among eligible Medicare beneficiaries with HFREF was low and highly variable. Areas with low use rates had higher co-payments than areas with high rates of early use. However, even after controlling for costs, geographic prescribing patterns had a significant impact on drug diffusion. Most early use was concentrated in the Northeast and South. The rate of increase in the West between 2016 and 2018 outpaced that of other regions such that by the end of 2018, use rates were more similar in the Northeast, South, and West, with the highest rates observed in the Northeast and the lowest in the Midwest. This variation highlights opportunities to expand the use of sacubitril/valsartan among eligible beneficiaries with HFREF and highlights the importance of local prescribing patterns in managing the diffusion of novel therapies into clinical practice. ■

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eAppendix A. National Drug Codes for Sacubitril/Valsartan

0078-0659-20

0078-0659-35

0078-0659-61

0078-0659-67

0078-0777-20

0078-0777-35

0078-0696-61

0078-0777-67

0078-0696-20

0078-0696-35

0078-0777-61

0078-0696-67

eAppendix B. Characteristics of Beneficiaries who Received Only 1 Fill of Sacubitril/Valsartan vs. Those With >1 Fill of Sacubitril/Valsartan, 2016-2018

	Only 1 Sacubitril/ Valsartan Fill		>1 Sacubitril/ Valsartan Fill		p- value
	N/Mean	%/SD	N/Mean	%/SD	
N	5514	26.69	15952	74.31	
Age	76.83	7.05	75.94	6.95	0.069
Female	1893	34.33	5510	34.54	0.777
Race					0.451
White	4692	85.09	13457	84.36	
Black	496	9.00	1502	9.42	
Hispanic	75	1.36	255	1.60	
Other	251	4.55	738	4.63	
Dual Eligibility	1076	19.51	3519	22.06	<0.001
Mean % Bachelor's Degree	23.64	14.21	23.20	13.99	0.417
Mean % Below Federal Poverty Level	9.38	6.38	9.59	6.72	0.652
Geographic Region					0.106
East South Central (AL, KY, MS, TN)	433	7.85	1338	8.39	
Middle Atlantic (NJ NY, PA)					
East North Central (WI, MI, IL, IN, OH)	912	16.54	2646	16.59	
Mountain (MT, ID, WY, NV, UT, CO, AZ, NM)	864	15.67	2454	15.38	
New England (ME, NH, VT, MA, CT, RI)	204	3.70	502	3.15	
Pacific (WA, OR, CA)	196	3.55	594	3.72	
South Atlantic (WV, MD, DE, VA, NC, SC, GA, FL)	607	11.01	1684	10.56	
West North Central (ND, SD, NE, KS, MN, IA, MO)	1312	23.79	3641	22.82	
West South Central (TX, OK, AR, LA)	282	5.11	871	5.46	
Urban/Rural					0.307
Urban	4698	85.20	13453	84.33	
Large Rural	421	7.64	1286	8.06	
Small Rural/Isolated	395	7.16	1213	7.60	
Heart Failure Severity					0.0743
% with no HF hospitalizations in year prior	4452	80.74	13044	81.77	
% with 1-2 HF hospitalizations in year prior	911	16.52	2547	15.97	
% with >2 HF hospitalizations in year prior	151	2.74	361	2.26	
*Concurrent MRA Use	1333	24.17	4057	25.43	0.063
*Concurrent Beta Blocker Use	3368	61.08	10556	66.17	<0.001
ACEi/ARB Use Prior to Admission	2307	41.84	8273	51.86	<0.001
Comorbidity Burden					
Coronary Artery Disease	5096	92.42	14500	90.90	<0.001
Chronic Kidney Disease	3886	70.48	10196	63.92	<0.001
Diabetes CCW Flag	3048	55.28	8539	53.53	0.025

% with ≥ 5 CCW Comorbidity Flags	5259	95.38	14901	93.41	<0.001
% with >30-day Inpatient/Post-Acute Care in year prior	70	1.27	165	1.03	0.148

HF is heart failure, MRA is mineralocorticoid receptor antagonist, CCW is chronic condition warehouse

*Concurrent use is defined as ≥ 1 fill in the 90 days prior to index admission and ≥ 1 fill after hospital discharge