ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

Trajectories of Sacubitril/Valsartan Adherence Among Medicare Beneficiaries With Heart Failure

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ABSTRACT

BACKGROUND Sacubitril/valsartan, an angiotensin receptor/neprilysin inhibitor (ARNi), improves heart failure (HF) outcomes, yet real-world adherence patterns are not well understood.

OBJECTIVES The purpose of this study was to analyze longitudinal patterns of adherence to ARNis in patients with HF and to identify factors associated with adherence patterns.

METHODS Using Medicare beneficiaries from 2015 to 2018, we included patients diagnosed with HF who initiated an ARNi. A group-based trajectory model was constructed to identify adherence patterns during follow-up. We used multivariable logistic regression to investigate factors associated with membership in each adherence trajectory group.

RESULTS Among 9,475 eligible beneficiaries (age 77 ± 7 years, 34% female), we identified 5 distinct ARNi adherence trajectories, characterized as: immediate discontinuers, who discontinued treatment within the first 3 months (12%); early discontinuers, who discontinued treatment in months 4 to 7 (10%); late discontinuers, who discontinued treatment in months 7 to 10 (12%); intermittently adherent patients (12%); and consistently adherent patients (54%). The first 4 groups were collectively categorized as nonconsistent adherents. Living in a socioeconomically disadvantaged area, ie, a county with the top 20% of Area Deprivation Index (adjusted OR [aOR]: 1.12 [95% CI: 1.00-1.24]) and Black race (aOR: 1.36, [95% CI: 1.18-1.56]) were associated with a higher likelihood of being nonconsistently adherent. Receiving prescriptions from a cardiologist (aOR: 0.64 [95% CI: 0.57-0.73]) was associated with a lower likelihood of suboptimal ARNi adherence.

CONCLUSIONS Half of ARNi users were not consistently adherent to the drug in the first year after treatment initiation. There exist significant racial and socioeconomic inequities in longitudinal adherence to ARNi. (JACC Adv 2024;3:100958) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ABBREVIATIONS AND ACRONYMS

aOR = adjusted odds ratio

ACEI = angiotensin-converting enzyme inhibitor

ADI = Area Deprivation Index

ARB = angiotensin receptor blocker

ARNi = angiotensin receptor/neprilysin inhibitor

BB = beta-blocker

CCB = calcium channel blockers

CCW = chronic conditions data warehouse

CHF = chronic heart failure

CKD = chronic kidney disease

CMS = Centers for Medicare and Medicaid Services

COPD = chronic obstructive pulmonary disease

ER = emergency room

HF = heart failure

PDC = proportion of days covered

PIA = positive inotropic agents

RUCC = Rural-Urban Continuum Codes

Heart failure (HF) is a prevalent condition affecting over 6 million Americans, and projections suggest that the number could rise to 8 million by 2030.[1] The incidence rate of HF approaches 10 per 1,000 population after the age of 65 years.[1] HF is also the second-leading cause of hospitalizations in the United States, resulting in more than 4.4 million hospital admissions and costing over $31 billion annually.[2]

Clinical trials have demonstrated that sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNi), can improve clinical outcomes in patients with chronic heart failure (CHF) by reducing the risk of hospitalizations and death.[3] ARNi was approved as a long-term treatment for CHF in the United States in 2015,[4] and it was recommended as a first-line therapy for CHF by the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines in 2017.[5] In the latest AHA/ACC/Heart Failure Society of American (HFSA) 2022 HF treatment guidelines, ARNi is recommended as first-line RASi to reduce morbidity and mortality in HF with reduced ejection fraction and HF with preserved ejection fraction.[6] Due to its efficacy and guideline recommendations, the uptake of ARNi has been steadily increasing.[7,8] A study utilizing data from the Veterans Health Administration suggested that 26% of veterans with HF with reduced ejection fraction who were renin-angiotensin-aldosterone system inhibitor naïve in 2019 initiated an ARNi.[7] Despite the benefits of ARNi therapy, adherence remains low among those who use it, limiting the potential for improving health outcomes in patients with HF.[9-11] For example, in patients from healthcare databases in Sweden, the UK, and the United States between 2016 and 2019, approximately 30% of ARNi users discontinued treatment within 1 year.[9] Furthermore, prior studies have elucidated that patients who identify as Black race or exhibit higher comorbidity burdens, or have lower household income are less likely to initiate or adhere to ARNi therapy.[12-14]

However, most of the previous studies only used the proportion of days covered (PDC) with ARNi as a single measure of adherence, which did not capture potentially important differences in patterns of longitudinal ARNi use. Patients with similar measures of PDC over a specific time period can have significant differences in underlying patterns of adherence.[15] These patterns may portend differential effectiveness of ARNi in improving CHF outcomes, and the underlying causes of suboptimal use may be different.
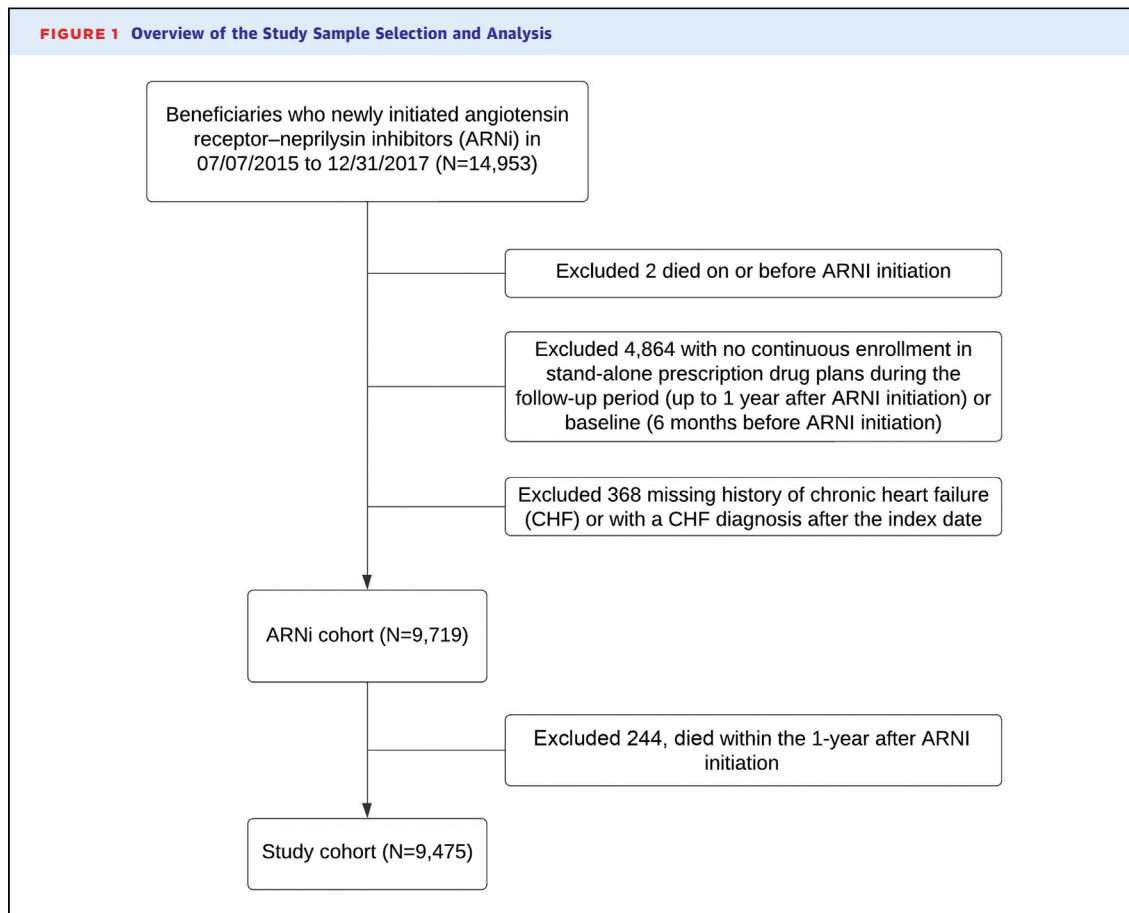
We aimed to characterize longitudinal patterns of ARNi adherence in patients with CHF and understand the impact of different factors on these patterns. To this end, we applied group-based trajectory models to Medicare data and identified distinct patient groups with similar adherence patterns in the year after treatment initiation. Furthermore, we examined different domains of factors associated with these longitudinal patterns, including patients' sociodemographic and clinical characteristics, healthcare utilization, and provider information.

METHODS

DATA SOURCES AND STUDY POPULATION. We conducted a retrospective cohort study using Medicare fee-for-service data from Parts A (inpatient coverage), B (outpatient coverage), D (prescription benefits), and chronic conditions data warehouse (CCW). Institutional review board approval (University of Florida Institutional Review Board reference #IRB201900262) was obtained before abstracting data.

We analyzed insurance claims data from a 15% random sample of national Medicare beneficiaries from the Centers for Medicare and Medicaid Services (CMS). Using Medicare Part D Event data, we created a cohort of ARNi treatment-naïve patients who were 65 years of age or older and initiated ARNi therapy between July 7, 2015 (ie, the date that sacubitril/valsartan entered the U.S. market) and December 31, 2017, and followed them for 360 days thereafter. The index date was defined as the date of the first ARNi prescription filled. We excluded patients who died before the first prescription fill date, those who did not have continuous enrollment in the fee-for-service plan for at least 6 months prior to the index date and throughout the 360-day follow-up period, those who did not have a CHF diagnosis based on the CMS CCW indicator of HF and nonischemic heart disease before or on the index date, those who died during the 360-day follow-up period (2.5%), and those who did not have continuous enrollment during follow-up to avoid missing data on the outcome (Figure 1).

STUDY OUTCOMES. Our primary outcome was the adherence trajectory of ARNi over the 1-year following initiation, which was operationally used by measuring PDC with ARNi during each 30-day interval after the patient's first ARNi prescription for a total of 360 days. All ARNi fills were arranged chronologically, and in cases of early refills, they were

FIGURE 1 Overview of the Study Sample Selection and Analysis

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┌─────────────────────────────────────────┐
│ Beneficiaries who newly initiated        │
│ angiotensin receptor–neprilysin          │
│ inhibitors (ARNi) in                     │
│ 07/07/2015 to 12/31/2017 (N=14,953)      │
└─────────────────────────────────────────┘
        │
        │      ┌──────────────────────────────────────────┐
        ├──────│ Excluded 2 died on or before ARNI initiation│
        │      └──────────────────────────────────────────┘
        │
        │      ┌──────────────────────────────────────────┐
        │      │ Excluded 4,864 with no continuous enrollment│
        ├──────│ in stand-alone prescription drug plans      │
        │      │ during the follow-up period (up to 1 year   │
        │      │ after ARNI initiation) or baseline (6 months │
        │      │ before ARNI initiation)                      │
        │      └──────────────────────────────────────────┘
        │
        │      ┌──────────────────────────────────────────┐
        │      │ Excluded 368 missing history of chronic     │
        ├──────│ heart failure (CHF) or with a CHF diagnosis │
        │      │ after the index date                        │
        │      └──────────────────────────────────────────┘
        ▼
┌─────────────────────────┐
│ ARNi cohort (N=9,719)   │
└─────────────────────────┘
        │
        │      ┌──────────────────────────────────────────┐
        ├──────│ Excluded 244, died within the 1-year after  │
        │      │ ARNI initiation                             │
        │      └──────────────────────────────────────────┘
        ▼
┌─────────────────────────┐
│ Study cohort (N=9,475)  │
└─────────────────────────┘
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added at the end of the preceding prescription. Using the fill date and days of supply (accounting for stock pills), we created a supply diary for each patient. We then calculated the PDC with ARNi for each 30-day interval as the ratio of the number of days covered with ARNi during that period (adjusted for inpatient stays as per Medicare guidelines) to the total number of days in the measurement period (also adjusted for inpatient stays).[16,17] Additionally, we calculated the PDC of ARNi over the entire 360-day period as a secondary outcome.

COVARIATES. Covariates were measured during the baseline period (6 months prior to and including the index date). We selected covariates based on previous adherence studies of cardiovascular medications.[14,15,18-22] The covariates comprised 4 categories: sociodemographics, clinical characteristics, healthcare utilization, and provider information. Sociodemographic variables included age, sex, and race/ethnicity, eligibility for Medicaid coverage, low-income subsidy receipt, rural or urban residence, and the geographic-based Area Deprivation Index

(ADI)[23] at the county level. The ADI is a continuous value with higher scores indicating areas with greater socio-economic disadvantage. We converted it to a dichotomized variable, with the highest ADI quintile defined as high area deprivation.[24] Patient's ADI was linked at the patient level, based on their Federal Information Processing Standards code. Rural or urban residence was identified using the Rural-Urban Continuum Codes (RUCC) linked with patients' Federal Information Processing Standards codes in the Medicare data. The RUCC, which categorizes counties based on population size, degree of urbanization, and proximity to metropolitan areas, were obtained from the U.S. Department of Agriculture website.[25] In this study, regions with RUCC codes 1 to 3 and 4 to 9 were categorized as urban and rural regions, respectively. Clinical characteristics included comorbidities (ie, acute myocardial infarction, Alzheimer disease, atrial fibrillation, cancer, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), depression, diabetes, stroke or transient ischemic attack identified using CMS CCW indicators), previous medications (ie, angiotensin-converting enzyme

inhibitor (ACEI), angiotensin receptor blocker (ARB), diuretics, beta-blocker, anticoagulants, calcium channel blockers (CCB), antidiabetic drug, positive inotropic agents, nitrates identified using Part D prescription claims), HF hospitalization within 6 months prior to the index date, and duration since HF diagnosis (identified using CMS Chronic Condition Warehouse indicators that trace the first diagnosis of the conditions date back to January 1, 1999). Healthcare utilization information included any emergency room (ER) visits, any hospitalizations, and total medication costs within 6 months prior to the index date. We also included information on prescribing provider specialty, determined by the provider who authored the initial prescription, and these providers were categorized into 3 groups: cardiologists, primary care physicians, and others.

STATISTICAL ANALYSIS. We presented descriptive statistics of baseline patient characteristics, reporting numbers and percentages for categorical variables, and mean $\pm$ SD or median (IQR) for continuous variables.

We utilized group-based trajectory modeling to classify patients into distinct adherence groups, taking into account their utilization of ARNi treatment over the initial 360 days.[15,18,20,21,26] Before modeling, we transformed the monthly PDC of ARNi using the arcsine transformation to meet the assumptions of the finite mixture trajectory model with a normal distribution for each trajectory.[26,27] The monthly PDC was then modeled with time represented in months since initiating treatment, ranging from 1 to 12. Each month was counted at 30-day intervals. We used the SAS procedure PROC TRAJ (an open sourced add-on package to SAS[28]) and used the most flexible functional form of time (allowing up to a fifth-order polynomial) to create the trajectory models as described previously.[29] The final model was selected based on the Bayesian information criteria, Nagin's criteria, sufficient number of beneficiaries in each trajectory group, and clinical relevance of trajectory patterns.[30] The model output includes a projected trajectory curve over time, group membership, and the estimated probabilities of membership of each group for each patient.[30]

We compared patient characteristics across trajectory groups using chi-square and ANOVA tests, as appropriate. We dichotomized trajectory groups into consistent adherent vs others (all other nonconsistent adherence groups) and constructed a multivariable logistic regression model to determine factors associated with consistent adherence to ANRi over time. To better understand the factors associated with the longitudinal adherence patterns, we also constructed

a multivariable logistic regression model regressing trajectory group membership on sociodemographic variables, clinical characteristics, health care utilization, and provider specialty (independent variables listed above). A backward selection procedure was employed for both models to choose the covariates to be included in the final models, with a *P* value for removal of 0.05.

We conducted a sensitivity analysis by limiting the group-based trajectory modeling to beneficiaries who had at least one refill during the follow-up period. All analyses were performed using SAS v9.4 (SAS Institute).

RESULTS

STUDY COHORT CHARACTERISTICS. A total of 9,475 eligible beneficiaries were included in the study cohort, with a mean age of 77.6 $\pm$ 7.3 years, 34.3% female, 75.9% White, 11.2% Black, 8.2% Hispanic, and 3.8% others. Among the cohort, the annual mean PDC was 58.8% $\pm$ 46.5%, and 89% refilled at least 1 prescription for ARNi in the 360 days after ARNi initiation. In the 6 months before cohort entry, about 95% of patients had an ER visit or hospitalization, with a HF hospitalization rate of 12% (**Table 1**).

ADHERENCE TRAJECTORIES. We identified 5 distinct trajectories of ARNi adherence (**Figure 2**): patients who stopped filling the ARNi prescriptions within the first 3 months ("Immediate Discontinuers," group 1, 12.7% of all patients; mean annual PDC 1% $\pm$ 10%); patients who discontinued treatment from months 4 to 7 post-ARNi initiation ("Early Discontinuers," group 2, 9.9%; annual mean PDC 4% $\pm$ 16%); patients who discontinued treatment from months 7 to 10 post-ARNi initiation ("Late Discontinuers," group 3, 11.5%; mean annual PDC 10% $\pm$ 26%); patients whose adherence fluctuated ("Intermittently Adherents," group 4, 12.0%; mean annual PDC 67% $\pm$ 38%); and patients who consistently maintained treatment throughout the 360 days ("Consistent Adherents," group 5, 53.8%; mean annual PDC 91% $\pm$ 24%). This 5-group model met all of Nagin's criteria, including having an average posterior probability of over 70%, narrow CIs for estimated probability, and odds of correct classification >5 for all 5 groups, as shown in Supplemental Table 1.

When we compared the trajectory group patterns from the full cohort to those from the sensitivity analysis (Supplemental Figure 1, Supplemental Table 2) that restricted the cohort to beneficiaries with at least 1 refill during the follow-up period, we found that ARNi adherence trajectory patterns were comparable except that the Immediate Discontinuers

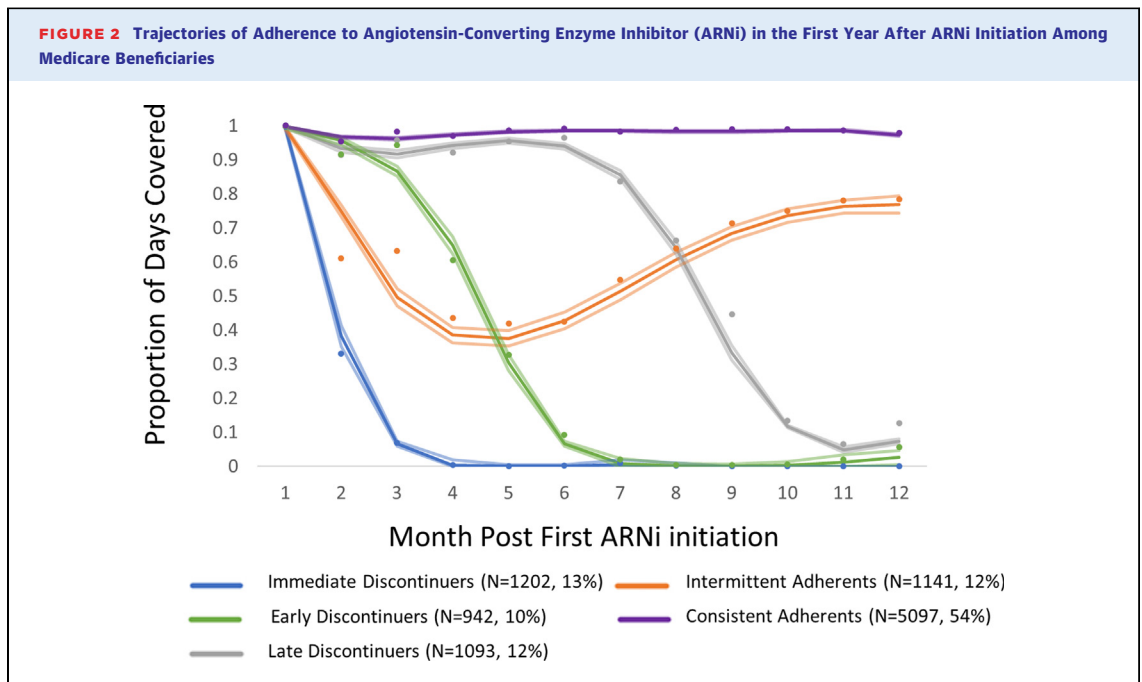**TABLE 1 Baseline Participants Characteristics by ARNi Trajectory Groups**

	Total (N = 9,475, 100%)	Immediate Discontinuers (n = 1,202, 12.69%)	Intermittent Adherents (n = 1,141, 12.04%)	Late Discontinuers (n =1,093, 11.54%)	Early Discontinuers (n = 942, 9.94%)	Consistent Adherents (n = 5,097, 53.79%)
Female	3,246 (34.26%)	417 (36.64%)	397 (35.35%)	387 (35.02%)	350 (35.71%)	1,695 (33.05%)
Age, y	76.57 ± 7.26	77.92 ± 7.74	75.63 ± 6.91	77.15 ± 7.46	77.38 ± 7.5	76.17 ± 7.06
Race						
Non-Hispanic White	7,191 (75.89%)	847 (74.43%)	771 (68.66%)	846 (76.56%)	747 (76.22%)	3,980 (77.60%)
Non-Hispanic Black	1,156 (12.2%)	175 (15.38%)	206 (18.34%)	122 (11.04%)	128 (13.06%)	525 (10.24%)
Hispanic	773 (8.16%)	85 (7.47%)	109 (9.71%)	85 (7.69%)	67 (6.84%)	427 (8.33%)
Other	355 (3.75%)	31 (2.72%)	37 (3.29%)	52 (4.71%)	38 (3.88%)	197 (3.84%)
Medicaid eligibility	2,874 (30.33%)	380 (33.39%)	396 (35.26%)	312 (28.24%)	283 (28.88%)	1,503 (29.30%)
Low-income subsidy eligibility	3,240 (34.2%)	419 (36.82%)	440 (39.18%)	350 (31.67%)	329 (33.57%)	1,702 (33.18%)
Region						
High area deprivation	1,851 (19.54%)	225 (19.77%)	262 (23.33%)	236 (21.36%)	197 (20.1%)	931 (18.15%)
Urban	7,902 (83.4%)	927 (81.46%)	919 (81.83%)	941 (85.16%)	843 (86.02%)	4,272 (83.29%)
HF duration, y	5.99 (5.17)	6.84 (5.48)	5.59 (4.9)	6.18 (5.17)	6.47 (5.27)	5.76 (5.1)
Age of HF diagnosis, y	70.57 ± 7.12	71.09 ± 8.07	70.05 ± 6.7	70.97 ± 7.21	70.91 ± 7.41	70.41 ± 6.89
Background therapy						
ACEI	2,177 (22.98%)	424 (37.26%)	197 (17.54%)	266 (24.07%)	291 (29.69%)	999 (19.48%)
ARB	1,582 (16.7%)	286 (25.13%)	118 (10.51%)	193 (17.47%)	249 (25.41%)	736 (14.35%)
Diuretics	7,770 (82.01%)	959 (84.27%)	918 (81.75%)	920 (83.26%)	835 (85.20%)	4,138 (80.68%)
Beta-blocker	8,645 (91.24%)	1,026 (90.16%)	996 (88.69%)	994 (89.95%)	871 (88.88%)	4,758 (92.77%)
Anticoagulants	2,429 (25.64%)	303 (26.63%)	280 (24.93%)	309 (27.96%)	258 (26.33%)	1,279 (24.94%)
Calcium-channel blockers	1,289 (13.6%)	221 (19.42%)	126 (11.22%)	138 (12.49%)	161 (16.43%)	643 (12.54%)
Antidiabetic drug	3,416 (36.05%)	422 (37.08%)	420 (37.40%)	403 (36.47%)	342 (34.90%)	1,829 (35.66%)
PIA	1,597 (16.85%)	201 (17.66%)	196 (17.45%)	170 (15.38%)	174 (17.76%)	856 (16.69%)
Nitrates	2,008 (21.19%)	297 (26.10%)	215 (19.15%)	239 (21.63%)	257 (26.22%)	1,000 (19.50%)
Comorbidity						
Acute myocardial infarction	2,177 (22.98%)	291 (25.57%)	240 (21.37%)	279 (25.25%)	271 (27.65%)	1,096 (21.37%)
Alzheimer disease	1,478 (15.6%)	256 (22.50%)	159 (14.16%)	223 (20.18%)	172 (17.55%)	668 (13.02%)
Atrial fibrillation	4,734 (49.96%)	610 (53.60%)	514 (45.77%)	564 (51.04%)	507 (51.73%)	2,539 (49.50%)
Cancer	1,703 (17.97%)	232 (20.39%)	185 (16.47%)	218 (19.73%)	192 (19.59%)	876 (17.08%)
Chronic kidney disease	6,271 (66.18%)	863 (75.83%)	759 (67.59%)	739 (66.88%)	724 (73.88%)	3,186 (62.12%)
Chronic obstructive pulmonary disease	4,918 (51.91%)	665 (58.44%)	602 (53.61%)	600 (54.30%)	557 (56.84%)	2,494 (48.63%)
Depression	3,759 (39.67%)	554 (48.68%)	470 (41.85%)	479 (43.35%)	414 (42.24%)	1,842 (35.91%)
Diabetes	5,902 (62.29%)	756 (66.43%)	697 (62.07%)	707 (63.98%)	641 (65.41%)	3,101 (60.46%)
Stroke/transient ischemic attack	8,959 (94.55%)	1,091 (95.87%)	1,056 (94.03%)	1,054 (95.38%)	926 (94.49%)	4,832 (94.21%)
History of heart failure hospitalization	1,138 (12.01%)	249 (21.88%)	134 (11.93%)	155 (14.03%)	164 (16.73%)	436 (8.50%)
Drug cost	272.02 (78.65, 576.69)	257.81 (65.88, 539.57)	222.45 (62.55, 555.27)	291.22 (83.08, 556.27)	274.645 (79.05, 598.69)	279.38 (84.7, 587.9)
History of ER visit or hospitalization	8,959 (94.55%)	1,091 (95.87%)	1,056 (94.03%)	1,054 (95.38%)	926 (94.49%)	4,832 (94.21%)
ARNI initiation prescriber specialty						
Cardiology	6,442 (67.99%)	641 (56.33%)	758 (67.50%)	713 (64.52%)	649 (66.22%)	3,681 (71.77%)
PCP	1,513 (15.97%)	323 (28.38%)	180 (16.03%)	204 (18.46%)	179 (18.27%)	627 (12.22%)
Others	1,520 (16.04%)	174 (15.29%)	185 (16.47%)	188 (17.01%)	152 (15.51%)	821 (16.01%)

Values are n (%), mean ± SD, or median (25th, 75th).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; CCB = calcium-channel blocker; PCP = primary care provider; PIA = positive inotropic agents; USD = U.S. dollar.

group observed in the overall cohort disappeared from the subcohort only including patients with ≥2 prescriptions filled.

The Immediate Discontinuers group had a higher proportion of women, longer HF duration on average, higher average age of HF diagnosis, higher proportion of patients who used ACEI or CCB within 6 months prior to ARNi initiation, a higher proportion of patients with various comorbidities such as Alzheimer disease, atrial fibrillation, cancer, CKD, COPD,

FIGURE 2 Trajectories of Adherence to Angiotensin-Converting Enzyme Inhibitor (ARNi) in the First Year After ARNi Initiation Among Medicare Beneficiaries

depression, diabetes, stroke/transient ischemic attack, as well as a higher proportion of patients who had ≥1 HF hospitalization, ER visit, or all-cause hospitalization within 6 months prior to ARNi initiation, compared to other trajectory groups. Additionally, patients in this group were more likely to be prescribed ARNi from a primary care physician (**Table 1**).

ASSOCIATION BETWEEN PATIENT CHARACTERISTICS AND GROUP TRAJECTORY MEMBERSHIP. Table 2 presents the adjusted results from the multivariable logistic regression models after a backward selection, with sex, age, and race forced into the model. The outcome was dichotomized as consistently adherent patients vs nonconsistently adherent patients (grouped the Immediate Discontinuers, Early Discontinuers, Late Discontinuers and Intermittent Adherents together). The adjusted ORs (aORs) represent the likelihood of belonging to a nonconsistent adherents group (any group other than consistent adherence) vs the consistent adherents trajectory group (ie, the reference group) (**Central Illustration**).

Demographic characteristics. Black patients were found to have a higher likelihood of suboptimal ARNi adherence (aOR: 1.36; 95% CI: 1.18-1.56).

Social determinants. Eligibility for Medicaid coverage (aOR: 0.81; 95% CI: 0.73-0.90) was associated with a lower likelihood of not consistently adhering to ARNi. On the other hand, living in a socioeconomically disadvantaged area, ie, a county with a high area deprivation (aOR: 1.12; 95% CI: 1.00-1.24), was

associated with a higher likelihood of being non-consistently adherent to ARNi.

Clinical factors. Use of baseline medications such as ACEI (aOR: 1.69; 95% CI: 1.53-1.87) or ARB (aOR: 1.54; 95% CI: 1.37-1.72), as well as having various comorbid conditions such as Alzheimer disease (aOR: 1.21; 95% CI: 1.07-1.37), CKD (aOR: 1.31; 95% CI: 1.19-1.44), COPD (aOR: 1.12; 95% CI: 1.03-1.22), depression (aOR: 1.21; 95% CI: 1.11-1.33), and stroke/transient ischemic attack (aOR 1.15; 95% CI, 1.04-1.27), were associated with a higher likelihood of being nonconsistently adherent to ARNi. Additionally, having HF hospitalization in the 6 months prior to ARNi initiation (aOR: 1.40; 95% CI: 1.21-1.60) was also associated with a higher likelihood of being nonconsistently adherent to ARNi. On the other hand, use of baseline medications such as beta-blockers (aOR: 0.64; 95% CI: 0.55-0.74), anticoagulants (aOR: 0.85; 95% CI: 0.78-0.93), and antidiabetic drugs (aOR: 0.90; 95% CI: 0.82-0.99) were associated with a lower likelihood of not consistently adhering to ARNi.

Health care utilization and provider characteristics. Having ER visits or hospitalizations in the 6 months prior to ARNi initiation (aOR: 1.52; 95% CI: 1.39-1.66) was associated with a higher likelihood of being non-consistently adherent to ARNi. However, receiving prescriptions from a cardiologist (aOR: 0.64; 95% CI: 0.57-0.73) was associated with a lower likelihood of not consistently adhering to ARNi.

In the multivariable logistic regressions (Table 3), we observed a similar pattern of results, that is, compared to the consistent adherents group, the other trajectory groups were more likely to be Black, living in neighborhoods with high area deprivation, having comorbidities (eg, CKD and depression), having high out-of-pocket costs, having a recent HF hospitalization or ER/hospital visit, and receiving prescriptions from a primary care physician.

DISCUSSION

To our knowledge, our study is the first to utilize a nationally representative sample of Medicare fee-for-service beneficiaries to examine the longitudinal patterns of ARNi adherence among patients with HF. Our study yielded 2 main findings. First, we identified 5 distinct trajectory groups of ARNi adherence in the first year after its initiation. Of the study cohort, only half (54%) of patients were consistently adherent to ARNi over the follow-up period; 12% were intermittently adherent; 13% were immediate discontinuers (among which 95% never refilled); 10% were early discontinuers (ie, at 4-7 months); and 12% were late discontinuers (ie, at 7-10 months). However, because our cohort was predicated on having ≥1 ARNi fill (thus not capturing individuals who were prescribed, but never filled, an ARNi), our estimates of half of patients being consistently adherent to ARNi therapy are likely an overestimate. Because drug adverse effects usually occur at the early stage of treatment, adverse effects after the initial ARNi fill may have prompted immediate and early discontinuation but were less likely related to the intermediate or late adherence trajectory groups. Future studies that integrate patient-reported data are needed to understand the underlying causes of different patterns of suboptimal use of ARNi. Second, we evaluated factors associated with the longitudinal adherence to ARNi and identified that significant racial and socioeconomic disparities exist in ARNi adherence. Clinical factors, healthcare utilization, and provider factors also significantly impacted the ARNi adherence trajectory.

The adherence of ARNi was reported using a single PDC measure in a few prior studies.[12,13,31] For example, 1 study conducted among CHF hospitalized patients reported a mean PDC of 40% for patients who initiated ARNi during the inpatient admission.[32] Another study reported that 60% of patients who initiated ARNi were adherent to this treatment 180 days after initiation.[12] Our findings are consistent with prior evidence that has suggested an overall low adherence to ARNi, which can limit the benefits of the

TABLE 2 Estimated Adjusted ORs for the Association Between Patient Characteristics and Trajectory Group Membership
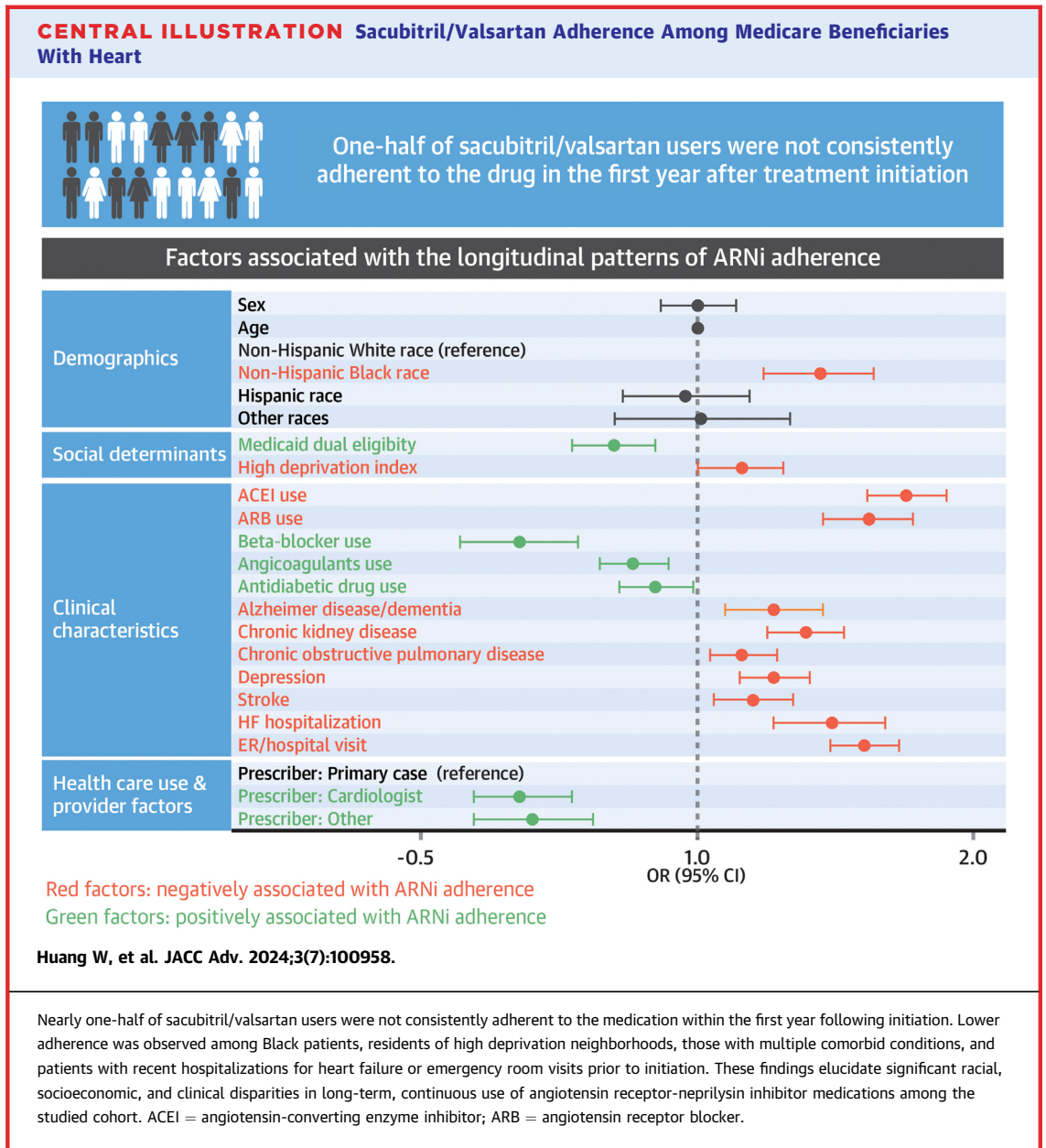
	Nonconsistent vs Consistent Adherents Group	
	OR (95% CI)	P Value
Sex	1.00 (0.91-1.10)	0.99
Age	1.00 (0.99-1.00)	0.58
Non-Hispanic White race	Reference	
Non-Hispanic Black race	1.36 (1.18-1.56)	<0.01
Hispanic race	0.97 (0.83-1.14)	0.73
Other races	1.01 (0.81-1.26)	0.96
Medicaid dual eligibility	0.81 (0.73-0.90)	<0.01
High area deprivation index[a]	1.12 (1.00-1.24)	0.05
ACEI use	1.69 (1.53-1.87)	<0.01
ARB use	1.54 (1.37-1.72)	<0.01
BB use	0.64 (0.55-0.74)	<0.01
Anticoagulants use	0.85 (0.78-0.93)	<0.01
Antidiabetic drug use	0.90 (0.82-0.99)	0.02
Alzheimer disease or dementia	1.21 (1.07-1.37)	<0.01
Chronic kidney disease	1.31 (1.19-1.44)	<0.01
Chronic obstructive pulmonary disease	1.12 (1.03-1.22)	0.01
Depression	1.21 (1.11-1.33)	<0.01
Stroke	1.15 (1.04-1.27)	0.01
Heart failure hospitalization	1.40 (1.21-1.60)	<0.01
ER or hospital visit	1.52 (1.39-1.66)	<0.01
Prescriber: primary care	Reference	
Prescriber: cardiologist	0.64 (0.57-0.73)	<0.01
Prescriber: other	0.66 (0.57-0.77)	<0.01

Results from a multivariable logistic regression model whose outcome was trajectory group (consistent adherents group set as reference) and predictors included all covariates listed in Table 1. Backward selection procedure was used to select predictors, using P value for stay = 0.05. The reference for each selected covariate is presented on the first column of the table. [a]High defined as top 20%.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; CCB = calcium-channel blocker; HF = heart failure.

treatment in improving HF outcomes in real-world patient populations. It is critical to understand the distinct patterns as well as the underlying causes of suboptimal adherence to this outcome-improving treatment for millions of patients with HF.

Our study is unique because, instead of capturing the overall adherence to ARNi with a single measure of PDC, we leveraged advanced group-based trajectory models to characterize longitudinal patterns of ARNi adherence over time. In doing so, we recognized significant disparities in the longitudinal adherence of ARNi. Black patients were 1.36 times less likely to be consistently adherent compared to White patients; patients living in socioeconomically disadvantaged areas were less likely to be consistently adherent compared to their more affluent counterparts. These findings are in line with prior research on racial and socioeconomic disparities in ARNi adherence.[12] It is noteworthy that in our study, eligibility for Medicaid coverage was associated with increased ARNi

CENTRAL ILLUSTRATION Sacubitril/Valsartan Adherence Among Medicare Beneficiaries With Heart

One-half of sacubitril/valsartan users were not consistently adherent to the drug in the first year after treatment initiation

Factors associated with the longitudinal patterns of ARNi adherence

Demographics
- Sex
- Age
- Non-Hispanic White race (reference)
- Non-Hispanic Black race
- Hispanic race
- Other races

Social determinants
- Medicaid dual eligibility
- High deprivation index

Clinical characteristics
- ACEI use
- ARB use
- Beta-blocker use
- Angicoagulants use
- Antidiabetic drug use
- Alzheimer disease/dementia
- Chronic kidney disease
- Chronic obstructive pulmonary disease
- Depression
- Stroke
- HF hospitalization
- ER/hospital visit

Health care use & provider factors
- Prescriber: Primary case (reference)
- Prescriber: Cardiologist
- Prescriber: Other

OR (95% CI): -0.5, 1.0, 2.0

Red factors: negatively associated with ARNi adherence
Green factors: positively associated with ARNi adherence

Huang W, et al. JACC Adv. 2024;3(7):100958.

Nearly one-half of sacubitril/valsartan users were not consistently adherent to the medication within the first year following initiation. Lower adherence was observed among Black patients, residents of high deprivation neighborhoods, those with multiple comorbid conditions, and patients with recent hospitalizations for heart failure or emergency room visits prior to initiation. These findings elucidate significant racial, socioeconomic, and clinical disparities in long-term, continuous use of angiotensin receptor-neprilysin inhibitor medications among the studied cohort. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

adherence. This finding is likely attributed, at least in part, to the 95% lower out-of-pocket costs faced by beneficiaries who are dually eligible for Medicare and Medicaid coverage compared to those without Medicaid coverage. These findings suggest the importance of lowering the economic burden of medications in order to improve adherence.[13] By recognizing these patients, clinicians can initiate conversations about financial barriers and explore strategies to mitigate the impact of socioeconomic disparities on medication adherence. This may involve collaborating with social workers, pharmacists, or utilizing patient assistance programs to ensure that patients have access to their prescribed medications.

Our study also found patient clinical characteristics and prescriber specialty associated with the longitudinal patterns of ARNi adherence. For example, we observed that patients with comorbidities (e.g., Alzheimer disease, CKD, COPD, depression, and stroke/transient ischemic attack) were more likely to have suboptimal ARNi adherence compared to those

TABLE 3 Adjusted ORs of Important Factors Associated With Group Trajectory Membership

	Immediate Discontinuers vs Consistent Adherents		Late Discontinuers vs Consistent Adherents		Intermittent Adherents vs Consistent Adherents		Early Discontinuers vs Consistent Adherents	
	Adjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Sex	1.04 (0.90-1.20)	0.59	0.99 (0.86-1.14)	0.89	1.00 (0.87-1.15)	0.98	0.94 (0.81-1.10)	0.47
Age	1.01 (1.00-1.01)	0.22	1.00 (0.99-1.01)	0.75	0.99 (0.98-0.99)[a]	<0.01	1.00 (0.99-1.01)	0.82
White race	Reference		Reference		Reference		Reference	
Black race	1.52 (1.23-1.87)[a]	<0.01	1.03 (0.82-1.30)	0.80	1.66 (1.36-2.03)[a]	<0.01	1.17 (0.92-1.48)	0.21
Hispanic race	0.82 (0.63-1.08)	0.15	0.91 (0.70-1.19)	0.51	1.40 (1.10-1.77)[a]	0.01	0.79 (0.59-1.06)	0.11
Other races	0.74 (0.50-1.10)	0.14	1.25 (0.90-1.73)	0.19	0.98 (0.68-1.41)	0.89	1.08 (0.75-1.56)	0.67
Medicare dual eligibility	0.86 (0.72-1.03)	0.10	0.71 (0.59-0.86)[a]	<0.01	0.88 (0.74-1.05)	0.17	0.80 (0.66-0.97)[a]	0.03
High Area Deprivation Index[b]	0.94 (0.78-1.13)	0.50	1.25 (1.04-1.49)[a]	0.02	1.19 (1.00-1.41)[a]	0.05	1.19 (0.98-1.45)	0.08
Region: rural	Reference		Reference		Reference		Reference	
Region: metro	0.87 (0.72-1.04)	0.13	1.21 (1.00-1.48)[a]	0.05	0.96 (0.80-1.16)	0.69	1.32 (1.06-1.64)[a]	0.01
ACEI use	2.75 (2.37-3.19)[a]	<0.01	1.39 (1.19-1.64)[a]	<0.01	0.79 (0.66-0.94)[a]	0.01	2.13 (1.80-2.51)[a]	<0.01
ARB use	2.17 (1.84-2.57)[a]	<0.01	1.30 (1.08-1.56)[a]	<0.01	0.67 (0.54-0.83)[a]	<0.01	2.33 (1.96-2.78)[a]	<0.01
BB use	0.63 (0.50-0.79)[a]	<0.01	0.68 (0.54-0.85)[a]	<0.01	0.64 (0.51-0.79)[a]	<0.01	0.55 (0.44-0.70)[a]	<0.01
Anticoagulants use	0.77 (0.67-0.89)[a]	<0.01	0.85 (0.74-0.97)[a]	0.02	0.90 (0.79-1.03)	0.13	0.92 (0.80-1.07)	0.30
CCB use	1.24 (1.04-1.48)[a]	0.02	0.85 (0.69-1.04)	0.11	0.83 (0.67-1.02)	0.08	1.05 (0.86-1.28)	0.67
Antidiabetic drug use	0.86 (0.75-0.99)[a]	0.04	0.99 (0.86-1.15)	0.91	0.93 (0.81-1.08)	0.35	0.79 (0.68-0.93)[a]	<0.01
Nitrate use	1.12 (0.95-1.31)	0.18	1.05 (0.89-1.24)	0.58	0.91 (0.77-1.08)	0.27	1.29 (1.09-1.53)[a]	<0.01
Alzheimer disease or dementia	1.29 (1.07-1.54)[a]	0.01	1.42 (1.18-1.71)[a]	<0.01	0.95 (0.77-1.17)	0.62	1.21 (0.98-1.48)	0.07
Chronic kidney disease	1.46 (1.24-1.71)[a]	<0.01	1.10 (0.94-1.27)	0.23	1.24 (1.07-1.44)[a]	<0.01	1.55 (1.31-1.83)	<0.01
Depression	1.35 (1.18-1.56)[a]	<0.01	1.17 (1.01-1.35)[a]	0.04	1.23 (1.07-1.41)[a]	<0.01	1.16 (0.99-1.35)	0.06
High out of pocket cost[b]	1.29 (1.09-1.53)[a]	<0.01	0.92 (0.77-1.10)	0.37	1.03 (0.86-1.22)	0.78	1.01 (0.83-1.22)	0.94
ER or hospital visit	1.82 (1.57-2.12)[a]	<0.01	1.46 (1.26-1.69)[a]	<0.01	1.31 (1.13-1.51)[a]	<0.01	1.44 (1.23-1.69)[a]	<0.01
HF hospitalization	1.51 (1.24-1.83)[a]	<0.01	1.30 (1.04-1.61)[a]	0.02	1.20 (0.96-1.50)	0.12	1.42 (1.14-1.77)[a]	<0.01
Prescriber: primary care	Reference		Reference		Reference		Reference	
Prescriber: cardiologist	0.47 (0.39-0.55)[a]	<0.01	0.70 (0.58-0.85)[a]	<0.01	0.83 (0.69-1.00)	0.06	0.76 (0.62-0.93)[a]	0.01
Prescriber: other	0.48 (0.39-0.60)[a]	<0.01	0.77 (0.61-0.97)[a]	0.03	0.84 (0.66-1.06)	0.14	0.70 (0.54-0.90)[a]	0.01

Results from a multivariable logistic regression model whose outcome was trajectory group (consistent adherents group set as reference) and predictors included all covariates listed in Table 1. Backward selection procedure was used to select predictors, using P value for stay = 0.05. The reference for each selected covariate is presented on the first column of the table. [a]Indicates statistically significant results. [b]High defined as top 20% quartile.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; CCB = calcium-channel blocker; HF = heart failure; ER = emergency room.

with a better health state. This finding was comparable to prior studies showing that the count of comorbidities was negatively associated with adherence to ARNi.[12,14] Interestingly, our data showed that baseline use of ACEI/ARB was associated with suboptimal adherence compared to nonusers, which contradicted the study by Bhatt et al[14] that showed patients who had previously used ACEI/ARB had a higher percentage of adherent days of ARNi. The difference in study design and patient characteristics may partially explain the difference in results as the ARNi patient population in the Bhattet al[14] 2022 study did not require patients to have a CHF diagnosis, which may have included a healthier cohort. In addition, we found that, compared to primary care providers, cardiology specialists were associated with a higher likelihood of consistent adherence. This trend may be explained by the fact that cardiologists frequently oversee patients with intricate health conditions, possibly leading to a heightened inclination for treatment adherence. These findings collectively contribute to a more nuanced understanding of ARNi treatment in a real-word setting and provide valuable insights for tailoring interventions aimed at improving adherence patterns.

Our study is subject to several limitations. Firstly, we obtained information on prescription fills from claims data; thus, we would not know whether the patients actually took the medication or not. Secondly, our study included only Medicare fee-for-service beneficiaries, and thus, the findings may not be generalizable to other populations such as Medicaid, Medicare Advantage, or commercial insurance enrollees. However, as 36% of CHF patients in the United States are covered under Medicare,[33] our study included the most relevant populations with HF. Thirdly, using insurance claims data, we were unable to measure important clinical factors such as

the NYHA functional classification, left ventricular ejection fraction, and B-type natriuretic peptide values. Additionally, our findings are confined to the time frame of 2015 to 2018 due to data availability, which limits our ability to capture any recent changes in the knowledge of appropriate patient selection for ARNi that may have occurred since that period. And considering we required continued enrollment during the follow-up period, it limited our exploration of how noncontinuous enrollment might impact adherence relative to other factors. Research should consider its effects in greater detail.

CONCLUSIONS

In summary, our study used group-based trajectory models to analyze longitudinal adherence patterns for Medicare recipients with CHF who initiated ARNi. We identified 5 distinct trajectories of adherence to the treatment, with just half of patients being included in the consistently adherent trajectory. We observed lower adherence among Black patients, those living in socioeconomically disadvantaged areas, those with high comorbidity burdens, and those with recent HF hospitalization or ER visits. Our findings highlight implementation gaps in the real-world use of ARNi and suggest that targeted interventions aimed at improving adherence in vulnerable patient populations may be necessary. These findings emphasize the need to explore strategies to improve adherence among these patient populations to optimize the benefits of ARNi therapy.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Our study demonstrates that nearly 50% of Medicare beneficiaries with congestive HF are not consistently adherent to newly initiated ARNi therapy over 1 year. Significant disparities exist, with lower adherence among Black patients, those in high-deprivation areas, highly comorbid patients, and those recently hospitalized.

TRANSLATIONAL OUTLOOK: These findings indicate a need to identify high-risk patients early and implement interventions to improve adherence. This may involve collaborating with pharmacists, social workers, and assistance programs to address financial barriers and ensure optimal adherence and outcomes with ARNi therapy.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.