Cureus
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Open Access Original Article

Published via Centro Médico Episcopal San Lucas - Research Channel

Sacubitril/Valsartan Versus Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Therapy: Rehospitalization Outcomes in a Predominantly Hispanic Population With Heart Failure

Received 09/30/2026
Review began 10/13/2026
Review ended 10/27/2026
Published 10/29/2026

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DOI: 10.7759/cureus.118783

Yomara Huertas Gómez [1], Robert Ferrer Macías [1], Sebastián I. Morales Cancio [2, 3], Paola Vega González [1], Laura Rivera Serrano [1], Marialexandra Addarich Figueroa [4], Eduardo Colón [1]

1. Internal Medicine Residency Program, Centro Médico Episcopal San Lucas, Ponce, PRI 2. Medicine, Universidad Central del Caribe, Bayamón, PRI 3. Research, Centro Médico Episcopal San Lucas, Ponce, PRI 4. Biological Sciences, Universidad Central de Bayamón, Bayamón, PRI

Corresponding author: Sebastián I. Morales Cancio, sebamorales113@gmail.com

Abstract

Background

Heart failure (HF) remains a major cause of hospitalization and rehospitalization. Although sacubitril/valsartan has demonstrated improved outcomes in patients with HF with reduced ejection fraction, evidence regarding its use and rehospitalization outcomes in Hispanic populations remains limited. This study evaluated rehospitalization outcomes and compared clinical outcomes between patients receiving sacubitril/valsartan and those receiving angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) therapy in a predominantly Hispanic population in Puerto Rico.

Methods

We conducted a retrospective cohort study of 419 adults hospitalized with HF at a tertiary care center in Puerto Rico between January 2022 and June 2025. Medication exposure was assessed at index admission and subsequent readmission. Outcomes included HF-related rehospitalization, length of stay (LOS), recurrent hospitalization frequency, and time between admissions. We also evaluated outcomes among patients who transitioned from ACEi/ARB therapy to sacubitril/valsartan between hospitalizations.

Results

Patients receiving sacubitril/valsartan had a higher proportion of left ventricular ejection fraction (LVEF) <41% than those receiving ACEi/ARB therapy at index admission (65% vs 40%) and readmission (52% vs 38%). The observed readmission proportion was lower with sacubitril/valsartan than with ACEi/ARB therapy (37% vs 40%; relative risk, 0.88), but the difference was not statistically significant (p = 0.596). Mean LOS was longer with sacubitril/valsartan at index admission (7.5 vs 5 days) and shorter at readmission (6 vs 7 days). Among patients initially receiving ACEi/ARB therapy, those who subsequently transitioned to sacubitril/valsartan had fewer mean readmissions (2.6 vs 3.1; p = 0.534) and a longer mean interval between admissions (538 vs 463 days; p = 0.283); neither difference was statistically significant.

Conclusions

Sacubitril/valsartan was used in patients with a higher prevalence of reduced ejection fraction and showed numerically favorable rehospitalization outcomes with ACEi/ARB therapy, although differences were not statistically significant.

Categories: Pharmacology, Cardiology, Internal Medicine
Keywords: guideline-directed medical therapy, heart failure, hispanic population, rehospitalization, sacubitril/valsartan

Introduction

Heart failure (HF) affects more than 64 million people worldwide and is associated with substantial healthcare utilization and recurrent hospitalization [1,2]. Recurrent hospitalizations are clinically important because they are associated with greater morbidity and mortality, impaired quality of life, and increased healthcare expenditures [1,2]. In the United States, HF is a leading reason for hospitalization among adults aged 65 years and older, and approximately one in four patients experiences readmission within 30 days after discharge [3]. Cardiovascular disease also remains a leading cause of mortality in Puerto Rico [4]. In addition, studies of Puerto Rican populations have documented unfavorable cardiovascular health profiles

and a high prevalence of cardiometabolic risk factors that may contribute to HF development and progression [5].

Pharmacological treatment of heart failure with reduced ejection fraction (HFrEF) has evolved with the development of guideline-directed medical therapy (GDMT). Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) became established therapies based on evidence demonstrating lower mortality and fewer HF hospitalizations [6]. More recently, angiotensin receptor-neprilysin inhibitor (ARNI) therapy has provided an additional therapeutic approach. In PARADIGM-HF, sacubitril/valsartan was associated with a 20% lower risk of cardiovascular death or HF hospitalization and a 16% lower risk of all-cause mortality compared with enalapril [7]. Sacubitril/valsartan combines blockade of the renin-angiotensin-aldosterone system with neprilysin inhibition, thereby increasing endogenous natriuretic peptide activity and promoting physiologic effects that include natriuresis and vasodilation while limiting adverse cardiac remodeling [8].

Sacubitril/valsartan entered clinical practice following US Food and Drug Administration approval in 2015 and is now recommended as Class I therapy for symptomatic HFrEF [6]. Nevertheless, adoption of ARNI therapy in routine care remains incomplete. Registry data consistently indicate that many eligible patients either do not receive ARNI therapy or do not reach recommended target doses, reflecting broader challenges in the implementation of GDMT across healthcare settings [9-11]. Barriers to treatment optimization occur at the patient, clinician, and health-system levels and may contribute to the persistent gap between evidence-based recommendations and their application in clinical practice [11,12].

Patients with HF encountered in routine clinical practice may differ substantially from participants enrolled in randomized clinical trials. They may have greater comorbidity burden, more advanced disease severity, renal dysfunction, and complex treatment-selection patterns that influence medication prescribing and subsequent clinical outcomes [9,13,14]. A recent large comparative-effectiveness study using US electronic health record data demonstrated that sacubitril/valsartan was associated with lower rates of all-cause, cardiovascular, and HF hospitalization relative to ACEi/ARB therapy among patients with de novo HFrEF [15]. Despite evidence from randomized trials and observational studies, data regarding ARNI use and rehospitalization outcomes among Hispanic patients remain limited [7,15-18]. Hispanic populations also remain underrepresented in HF clinical research, limiting the evidence available to inform treatment implementation in these communities [16,17].

Understanding how guideline-directed therapies are implemented and associated with outcomes in routine clinical practice is particularly important because treatment decisions are influenced by patient complexity, clinician practice patterns, and healthcare system factors [11,12]. Given the clinical and economic burden of recurrent HF hospitalizations, evaluating these outcomes in populations underrepresented in HF research remains clinically relevant.

This study aimed to evaluate HF-related rehospitalization and associated hospitalization outcomes, including length of stay (LOS), recurrent hospitalization frequency, and time from discharge to readmission, among hospitalized patients with HF and to compare HF readmission risk between patients treated with sacubitril/valsartan and those treated with ACEi or ARBs in a predominantly Hispanic population in Puerto Rico. The primary comparison evaluated the association between medication exposure and HF-related readmission using relative risk estimates, with readmissions assessed during the available study period without restriction to a prespecified follow-up interval. We hypothesized that sacubitril/valsartan therapy would be associated with a lower risk of HF readmission and more favorable hospitalization outcomes compared with ACEi/ARB therapy.

Materials And Methods

Study design and setting

This retrospective cohort study was conducted at a tertiary care center in Puerto Rico and included HF hospitalizations from January 1, 2022, through June 15, 2025. Using longitudinal electronic medical record data, we evaluated medication exposure and subsequent hospitalization outcomes among patients receiving sacubitril/valsartan or ACEi or ARBs. Treatment assignment was not determined by the investigators; medication exposure reflected routine clinical care. Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.

Study population

Adult patients aged ⩾18 years with a primary diagnosis of HF during the study period were eligible for inclusion. Potentially eligible patients were identified from a predefined list generated for this study. HF diagnoses were identified using International Classification of Diseases, Tenth Revision (ICD-10) codes and confirmed through review of clinical documentation, including physician notes, imaging findings, and echocardiographic data when applicable. Patients were excluded if a diagnosis of HF could not be confirmed or if the available medical record was insufficient for the variables required for analysis.

Records were reviewed sequentially from the predefined patient list; however, because data collection concluded before the entire source list could be reviewed, not all potentially eligible records from the study period were screened. A total of 419 patients meeting the eligibility criteria were included in the final analytic cohort. No a priori sample size calculation was performed; the final sample size reflected the completed medical record review.

At index admission, patients were categorized as receiving sacubitril/valsartan, ACEi/ARB, or neither therapy. The sacubitril/valsartan cohort comprised patients documented as receiving sacubitril/valsartan at index admission, whereas the ACEi/ARB cohort comprised patients documented as receiving an ACEi or ARB at index admission. Patients receiving neither therapy were retained as a separate category but were not included in the primary comparison between the sacubitril/valsartan and ACEi/ARB cohorts.

Medication status was reassessed at subsequent readmission to evaluate changes in documented therapy over time. For the transition analysis, patients receiving ACEi/ARB therapy at index admission who were subsequently documented as receiving sacubitril/valsartan during a later readmission or at discharge from that hospitalization were classified as the ACEi/ARB-to-sacubitril/valsartan transition subgroup. Patients receiving ACEi/ARB therapy at index admission who were not subsequently documented as receiving sacubitril/valsartan constituted the non-transition subgroup for this analysis. The exact date of sacubitril/valsartan initiation was not available; therefore, this classification reflects a change in documented pharmacotherapy between hospitalization time points rather than the precise timing of treatment initiation.

Data sources and variable definitions

Data were extracted from the institutional electronic medical record system (MEDITECH) and de-identified using unique study codes. Collected variables included age, sex, body mass index (BMI), hypertension, diabetes mellitus, coronary artery disease (CAD), chronic kidney disease (CKD), hyperlipidemia, hypothyroidism, cerebrovascular accident (CVA), and peripheral artery disease. Clinical and laboratory variables included white blood cell count, red blood cell count, hemoglobin, hematocrit, peripheral oxygen saturation (SpO2), N-terminal pro-B-type natriuretic peptide (NT-proBNP), sodium, potassium, creatinine, systolic and diastolic blood pressure, C-reactive protein (CRP), and troponin status. The first available clinical and laboratory measurements obtained at admission were used for analysis.

Left ventricular ejection fraction (LVEF) was obtained from the first available echocardiographic assessment associated with the hospitalization and categorized as <41%, 41%-49%, or >49%. Unavailable LVEF measurements were classified as “not reported.”

Hospitalization-related variables included LOS during the index admission and subsequent readmission, 30-day-HF-related readmission, and the interval from discharge to subsequent HF readmission. The index admission was defined as the first qualifying hospitalization for HF identified for each patient during the study period, whereas readmission was defined as a subsequent hospitalization for HF following the index admission. LOS was determined using the recorded admission and discharge dates.

Medication exposure was obtained from physician discharge summaries and medication reconciliation records and evaluated separately at index admission and subsequent readmission. Potential confounders included age, sex, BMI, comorbidities, renal function, and LVEF. Because the primary comparisons were unadjusted, these factors were considered potential sources of confounding when interpreting the findings rather than covariates in an adjusted model.

Exposure and outcomes

The primary exposure of interest was HF pharmacotherapy at the time of hospitalization, categorized as sacubitril/valsartan, ACEi/ARB, or neither. The primary outcome was HF-related rehospitalization, defined as a subsequent HF hospitalization following the index admission during the study period, without restriction to a prespecified follow-up interval. Readmissions were ascertained from the institutional electronic medical record; therefore, HF hospitalizations occurring outside the study institution were not captured. Thirty-day HF-related readmission was summarized descriptively and defined as an HF hospitalization occurring within 30 days after discharge from the index hospitalization.

Secondary outcomes included LOS, recurrent hospitalization frequency, and the interval from discharge to readmission. LOS was calculated from recorded admission and discharge dates. For patients with multiple qualifying HF hospitalizations, each subsequent hospitalization was considered a readmission following the immediately preceding qualifying hospitalization. The interval to readmission was calculated from the discharge date of the preceding qualifying HF hospitalization to the admission date of the subsequent qualifying HF hospitalization. Recurrent hospitalization frequency represented the number of subsequent qualifying HF hospitalizations identified during the study period.

In-hospital mortality during the index hospitalization was captured during data collection; however, post-discharge mortality was not available, and mortality was not evaluated as a study outcome. Patients without

a documented readmission during the study period were excluded from analyses of the interval to readmission.

Statistical analysis

Continuous variables were summarized using means and standard deviations, and categorical variables were reported as frequencies and percentages. Independent-samples t tests were used to compare continuous variables between two independent treatment groups. Pearson's chi-square tests were used to evaluate associations between categorical variables when expected cell counts were adequate, whereas Fisher's exact test was used when expected cell counts were small. Differences in the overall distribution of LVEF categories between the ACEi/ARB and sacubitril/valsartan groups were evaluated separately at index admission and readmission using Pearson's chi-square tests. Readmission proportions according to medication exposure were evaluated using Pearson's chi-square analysis, with relative risk estimated for the comparison of readmission outcomes between medication groups. Comparisons of the mean number of readmissions and mean interval from discharge to subsequent readmission between patients who transitioned from ACEi/ARB therapy to sacubitril/valsartan and those who did not transition were performed using independent-samples t tests.

Missing data were handled using a complete-case approach for applicable analyses; however, unavailable LVEF measurements were retained as a separate "not reported" category in analyses of LVEF distribution. Two-sided p-values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 29.0.2.0 (Released 2022; IBM Corp., Armonk, NY, USA).

Ethical considerations

The study was approved by the Institutional Review Board (Approval No. 2503253404; approval date: April 14, 2025). The requirement for informed consent was waived because of the retrospective design and use of de-identified data.

Results

Baseline characteristics

A total of 419 patients meeting the eligibility criteria were included in the final analytic cohort. The mean age was 72.93 ± 12.23 years, and 258 (62%) patients were male. Demographic and clinical characteristics are summarized in Table *1*. The most prevalent comorbidity was hypertension (362 (86%)), followed by diabetes mellitus (253 (60%)), coronary artery disease (219 (52%)), and chronic kidney disease (159 (38%)).

Characteristics	Value
Age, years	72.93 ± 12.23
BMI, kg/m^2	28.73 ± 8.06
Female	161 (38%)
Male	258 (62%)
Hypertension	362 (86%)
Diabetes mellitus	253 (60%)
Coronary artery disease	219 (52%)
Chronic kidney disease	159 (38%)
Hyperlipidemia	103 (25%)
Hypothyroidism	96 (23%)
Cerebrovascular accident	33 (8%)
Peripheral artery disease	30 (7%)

TABLE 1: Baseline Demographic and Clinical Characteristics of the Study Population (N = 419)

Data are presented as mean ± standard deviation or n (%), unless otherwise indicated.

BMI, body mass index

Clinical, laboratory, and cardiac characteristics

Baseline clinical, laboratory, and cardiac function characteristics are summarized in Table *2*. Mean creatinine was 2.0 ± 2.2 mg/dL, and mean NT-proBNP was 1385.8 ± 140.0 pg/mL. LVEF <41% was documented in 177 patients (42%), while 161 patients (38%) had a positive troponin result.

Characteristics	Value
WBC, x10^3/µL	9.01 ± 4.0
RBC, x10^6/µL	4.10 ± 0.8
Hemoglobin, g/dL	11.9 ± 2.3
Hematocrit, %	37.2 ± 15.0
SpO_2, %	95.6 ± 4.7
NT-proBNP, pg/mL	1385.8 ± 140.0
Sodium, mEq/L	139.0 ± 4.7
Potassium, mEq/L	4.8 ± 2.1
Creatinine, mg/dL	2.0 ± 2.2
Systolic BP, mm Hg	133.9 ± 26.6
Diastolic BP, mm Hg	74.2 ± 14.6
CRP, mg/L	7.8 ± 7.8
Troponin negative	197 (47%)
Troponin positive	161 (38%)
Troponin not reported	61 (15%)
LVEF; <41%	177 (42%)
LVEF; 41-49%	41 (10%)
LVEF; >49%	89 (21%)
LVEF; Not reported	112 (27%)

TABLE 2: Baseline Clinical, Laboratory, and Cardiac Function Characteristics (N = 419)

Data are presented as mean ± standard deviation or n (%), unless otherwise indicated.

BP, blood pressure; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RBC, red blood cell count; SpO2, peripheral oxygen saturation; WBC, white blood cell count

LVEF by medication exposure

LVEF distributions according to medication exposure at index admission and readmission are summarized in Table 3. Patients receiving sacubitril/valsartan had a higher proportion of LVEF <41% than those receiving ACEi/ARB therapy at both index admission (68 (65%) vs 99 (40%)) and readmission (39 (52%) vs 27 (38%)). The overall LVEF distribution differed significantly between medication groups at both index admission ($p < 0.001$) and readmission ($p = 0.001$).

Hospitalization	Treatment group	<41%, n (%)	41%-49%, n (%)	>49%, n (%)	Not reported, n (%)	p-value
Index admission	ACEi/ARB (n = 250)	99 (40%)	28 (11%)	59 (24%)	64 (26%)	<0.001
	Sacubitril/valsartan (n = 105)	68 (65%)	4 (4%)	6 (6%)	27 (26%)	
Readmission	ACEi/ARB (n = 72)	27 (38%)	11 (15%)	18 (25%)	16 (22%)	0.001
	Sacubitril/valsartan (n = 75)	39 (52%)	2 (3%)	7 (9%)	27 (36%)	

TABLE 3: LVEF Distribution by Medication Exposure at Index Admission and Readmission

Data are presented as n (%). p-values were derived using Pearson's chi-square tests comparing the overall distribution of LVEF categories between medication groups at index admission and readmission. Index admission refers to the first qualifying HF hospitalization during the study period; readmission refers to a subsequent HF hospitalization.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; LVEF, left ventricular ejection fraction

Clinical outcomes by medication exposure

Overall, 147 of 419 patients (35.1%) experienced at least one HF-related readmission during the study period. Among patients who were readmitted, 29 of 147 (19.7%) experienced an HF-related readmission within 30 days of discharge from the index hospitalization, corresponding to 6.9% of the overall cohort. Clinical outcomes according to HF pharmacotherapy are summarized in Table *4*. Patients treated with sacubitril/valsartan had a lower observed proportion of readmissions than those receiving ACEi/ARB therapy (39 (37%) vs 101 (40%)), corresponding to a relative risk of 0.88. However, this difference was not statistically significant (p = 0.596). Mean LOS at index admission was longer among patients receiving sacubitril/valsartan than among those receiving ACEi/ARB therapy (7.5 vs 5 days), whereas mean LOS at readmission was shorter (6 vs 7 days).

Treatment Group	Index LOS, days	Readmission LOS, days	Readmission, n (%)	No readmission, n (%)	RR	p-value
ACEi/ARB (n = 250)	5	7	101 (40%)	149 (60%)	Reference	-
Sacubitril/valsartan (n = 105)	7.5	6	39 (37%)	66 (63%)	0.88	0.596

TABLE 4: Clinical Outcomes by Medication Exposure

Data are presented as mean or n (%), as applicable. The RR and corresponding p-value compare readmission outcomes for sacubitril/valsartan relative to ACE/i/ARB therapy. Index admission refers to the first qualifying HF hospitalization during the study period; readmission refers to subsequent HF hospitalization.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; LOS, length of stay; RR, relative risk

Outcomes following transition to sacubitril/valsartan

Outcomes among patients initially receiving ACEi/ARB therapy who subsequently transitioned to sacubitril/valsartan are summarized in Table *5*. Of the patients included in this analysis, 39 transitioned to sacubitril/valsartan and 124 did not. Patients who transitioned to sacubitril/valsartan had a lower mean number of readmissions than those who did not transition (2.6 vs 3.1; p = 0.534). The mean interval from discharge to subsequent readmission was also longer among patients who transitioned to sacubitril/valsartan (538 vs 463 days; p = 0.283). Neither difference was statistically significant.

Outcome	Transitioned to sacubitril/valsartan (n = 39)	No transition to sacubitril/valsartan (n = 124)	p-value
Number of readmissions, mean	2.6	3.1	0.534
Time between admissions, days, mean	538	463	0.283

TABLE 5: Outcomes by Transition to Sacubitril/Valsartan

Data are presented as means. The analysis was restricted to patients receiving ACEi/ARB therapy at index admission. Transition was defined as documented ACEi/ARB therapy at index admission followed by documented sacubitril/valsartan therapy during a subsequent readmission or at discharge from that hospitalization. p-values represent comparisons between the transition and no-transition groups and were derived using independent-sample t tests.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

Discussion

In this retrospective cohort of 419 hospitalized patients with HF in Puerto Rico, medication groups differed notably in baseline cardiac function, with reduced LVEF occurring more frequently among patients receiving sacubitril/valsartan than among those receiving ACEi/ARB therapy. Despite this difference, the sacubitril/valsartan group had a numerically lower proportion of readmissions, although the comparison did not reach statistical significance. Descriptively, this group also had a shorter mean LOS at readmission, while patients who transitioned from ACEi/ARB therapy to sacubitril/valsartan experienced fewer recurrent admissions and longer intervals from discharge to subsequent readmission.

As demonstrated in Table *1*, the study population reflected a high-risk HF cohort with significant cardiometabolic comorbidity. Hypertension, diabetes mellitus, coronary artery disease, and chronic kidney disease were highly prevalent, consistent with the elevated cardiovascular risk profile described in Puerto Rican and Hispanic populations [5]. These comorbidities may contribute to rehospitalization risk, influence treatment selection, and complicate the implementation of guideline-directed HF therapy in routine clinical practice. Importantly, this study provides data from a predominantly Hispanic Puerto Rican population, a demographic historically underrepresented in major randomized HF trials [16].

Baseline laboratory and cardiac function findings summarized in Table *2* further characterized the clinical complexity of the study population. Elevated NT-proBNP levels, impaired renal function, and a high prevalence of reduced ejection fraction were consistent with substantial clinical severity and cardiorenal disease. Troponin positivity was also common, potentially reflecting myocardial injury or stress among hospitalized patients.

Patients treated with sacubitril/valsartan had a higher prevalence of reduced LVEF than those treated with ACEi/ARB therapy at both index admission and readmission (Table *3*). This pattern may reflect treatment selection according to HF phenotype and disease severity, given that ARNI therapy is an established component of guideline-directed therapy for patients with HFrEF [6]. However, the reasons underlying individual prescribing decisions were not captured and cannot be directly determined. Real-world studies have demonstrated variable implementation of ARNI therapy and important differences in the clinical characteristics of patients receiving guideline-directed HF therapy [9-11]. These baseline differences are particularly relevant when interpreting outcomes in a nonrandomized cohort because treatment groups may differ systematically in factors associated with prognosis [13].

Clinical outcome analyses summarized in Table *4* showed differences in LOS patterns between the treatment groups. Mean LOS during the index admission was longer among patients receiving sacubitril/valsartan than among those receiving ACEi/ARB therapy (7.5 vs 5 days). Given the greater prevalence of reduced LVEF in the sacubitril/valsartan group, this difference may reflect underlying clinical complexity rather than an adverse association with therapy itself. Conversely, mean LOS during readmission was numerically shorter among patients receiving sacubitril/valsartan (6 vs 7 days). Because statistical testing of these LOS differences was not available, they should be interpreted descriptively and not as evidence of an independent treatment effect.

When examining readmission outcomes (Table *4*), patients receiving sacubitril/valsartan had a numerically lower readmission proportion than patients receiving ACEi/ARB therapy (39 (37%) vs 101 (40%)); however, the difference was not statistically significant (p = 0.596). The relative risk estimate of 0.88 was directionally consistent with a lower observed readmission risk in the sacubitril/valsartan group; however, the absence of statistical significance precludes a definitive conclusion regarding reduced rehospitalization in this cohort. This finding should therefore be considered hypothesis-generating and warrants further evaluation in this

population [7,15,19].

The transition analysis provided an additional perspective on longitudinal treatment patterns (Table *5*). Among patients initially receiving ACEi/ARB therapy, those who subsequently transitioned to sacubitril/valsartan had a lower mean number of readmissions (2.6 vs 3.1) and a longer mean interval from discharge to subsequent readmission (538 vs 463 days) than those who did not transition to sacubitril/valsartan. However, neither comparison was statistically significant ($p = 0.534$ and $p = 0.283$, respectively). Although changes in documented therapy could be identified across hospitalization time points, the exact timing of sacubitril/valsartan initiation was unavailable. Therefore, the observed differences cannot establish a temporal or causal relationship between sacubitril/valsartan initiation and subsequent hospitalization outcomes. These findings should instead be interpreted as descriptive differences in longitudinal treatment patterns that warrant further investigation in adequately powered prospective studies.

Taken together, our findings illustrate the challenges of evaluating guideline-directed HF therapy in routine clinical practice. Sacubitril/valsartan was used in patients with a greater prevalence of reduced LVEF, while several hospitalization outcomes were numerically favorable despite the absence of statistically significant differences. Given the substantial differences in LVEF between treatment groups and the unadjusted nature of the outcome comparisons, these findings should not be interpreted as evidence of a treatment effect and may reflect differences in HF phenotype, disease severity, treatment selection, or other measured and unmeasured confounders. Randomized trials have established the clinical benefits of sacubitril/valsartan in appropriately selected patients with HFrEF [7,19], whereas observational studies provide complementary information regarding how these therapies are implemented across more heterogeneous clinical populations [9,15,18]. Our findings extend this discussion to a predominantly Hispanic Puerto Rican cohort and highlight the need for further evaluation of guideline-directed HF therapy in populations that have historically been underrepresented in major HF trials [16].

This study has several limitations. The retrospective observational design limits causal inference and is subject to residual confounding, particularly confounding by indication. Because medication selection was not randomized, differences in underlying HF phenotype, disease severity, and other measured or unmeasured clinical characteristics may have influenced both treatment selection and outcomes. The study was conducted at a single tertiary care center in Puerto Rico, which may limit generalizability to healthcare systems with different patient populations and practice patterns. Readmissions were ascertained from the institutional electronic medical record; therefore, hospitalizations occurring outside the study institution were not captured. In addition, because patients entered the cohort at different times, potential follow-up duration varied according to the timing of each patient's index admission. Although in-hospital mortality during the index hospitalization was captured, post-discharge mortality was not available and therefore could not be accounted for as a competing event in the assessment of rehospitalization. Additionally, because data collection concluded before all potentially eligible records were reviewed, selection bias cannot be excluded, and the final cohort may not fully represent all patients hospitalized with HF during the study period.

Several clinical variables, including LVEF and troponin data, were incomplete for a subset of patients. Missing data were handled using a complete-case approach for applicable analyses; however, incomplete documentation may have introduced additional selection bias. HF phenotype was not evaluated in subgroup analyses despite clinically relevant differences in LVEF between treatment groups.

Outpatient medication adherence, the exact timing of medication initiation, socioeconomic variables, medication affordability, and healthcare access factors could not be fully assessed and may have influenced rehospitalization outcomes. Medication exposure was determined from documented therapy at hospitalization time points and therefore may not fully reflect longitudinal outpatient treatment persistence or adherence. The primary outcome comparisons were also unadjusted for baseline differences between treatment groups. Given the substantial differences in LVEF, this limits the ability to distinguish treatment-associated differences from differences in HF phenotype, disease severity, treatment selection, or other confounding factors. Finally, the relatively modest sample size may have limited statistical power to detect differences in hospitalization outcomes between treatment groups.

Conclusions

In this predominantly Hispanic population with HF, patients receiving sacubitril/valsartan had a higher prevalence of reduced LVEF than those receiving ACEi/ARB therapy. Patients receiving sacubitril/valsartan had a numerically lower observed risk of HF readmission than those receiving ACEi/ARB therapy; however, the difference was not statistically significant. These findings should be interpreted cautiously given the unadjusted comparisons, baseline differences in LVEF, potential confounding related to treatment selection, and the observational study design. Larger prospective studies are needed to further evaluate guideline-directed HF therapy and its association with rehospitalization outcomes in Hispanic populations.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Sebastián I. Morales Cancio, Yomara Huertas Gómez, Robert Ferrer Macías, Marialexandra Addarich Figueroa, Eduardo Colón, Laura Rivera Serrano, Paola Vega González

Acquisition, analysis, or interpretation of data: Sebastián I. Morales Cancio, Yomara Huertas Gómez, Robert Ferrer Macías, Marialexandra Addarich Figueroa, Laura Rivera Serrano, Paola Vega González

Drafting of the manuscript: Sebastián I. Morales Cancio, Robert Ferrer Macías, Marialexandra Addarich Figueroa

Critical review of the manuscript for important intellectual content: Sebastián I. Morales Cancio, Yomara Huertas Gómez, Robert Ferrer Macías, Eduardo Colón, Laura Rivera Serrano, Paola Vega González

Supervision: Yomara Huertas Gómez, Eduardo Colón, Laura Rivera Serrano, Paola Vega González

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Ponce Research Institute (PRI) IRB Committee issued approval 2503253404. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

Generative artificial intelligence tools (ChatGPT (OpenAI) and Claude (Anthropic)) were used to assist with language editing, including grammar, syntax, and transitions. All AI-assisted content and identified sources were independently reviewed and verified by the authors. The authors approved all revisions and remain fully responsible for the content, interpretation, and conclusions of the manuscript.

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