Comparing Healthcare Resource Utilization and Costs in HFpEF patients using SGLT2-inhibitor Combination Treatments: A Retrospective Claims Analysis

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Abstract

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Background: Heart failure with preserved ejection fraction (HFpEF) represents an increasingly significant clinical burden. Recent treatment guidelines recommend sodium-glucose cotransporter-2 inhibitors (SGLT2i) as foundational therapy, with the addition of either mineralocorticoid receptor antagonists (MRAs) or angiotensin receptor-neprilysin inhibitors (ARNIs) as adjunctive therapy. However, real-world evidence comparing healthcare resource utilization (HCRU) and costs between these combination therapies remains limited.

Methods: We conducted a retrospective cohort study using the Merative™ MarketScan® commercial and Medicare databases from 2019 to 2023 to compare HCRU and costs in adult patients (≥18 years) with HFpEF initiating SGLT2i+MRA vs. SGLT2i+ARNI. Patients required SGLT2i usage and continuous enrollment for 12 months pre- and post-index. Those using both MRA and ARNI concurrently were excluded. Outcomes assessed over 12 months post-initiation included inpatient (IP), emergency department (ED), outpatient (OP) services, and pharmacy costs. Multivariable regression models adjusted for demographic and clinical covariates.

Results: The study included 2,128 patients (1,418 MRA, 710 ARNI). Adjusted analyses showed that the ARNI group experienced significantly lower HCRU, including 9% fewer IP admissions (IRR, 0.91; 95% CI, 0.84-0.98; p=0.015), 20% shorter IP length of stay (IRR, 0.80; 95% CI, 0.72-0.89; p<0.001), 12% fewer ED visits (IRR, 0.88; 95% CI, 0.79-0.98; p=0.0164), and 11% fewer OP service days (IRR, 0.89; 95% CI, 0.84-0.95; p<0.001). Unadjusted mean total healthcare costs were modestly lower in the ARNI group compared to the MRA group, driven by reduced IP, ED, OP, and total costs, despite slightly higher pharmacy costs largely attributable to differences in drug prices. However, no statistically significant differences were observed in adjusted total healthcare costs across settings.

Conclusions: In this real-world analysis, adjunctive ARNI therapy was associated with reduced HCRU but did not translate into lower overall healthcare costs compared to MRA-based combination therapy. These findings highlight the importance of considering both utilization patterns and drug costs when selecting combination treatments for HFpEF, supporting the need for individualized treatment strategies, particularly in patients with multiple comorbidities.

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1. BACKGROUND

Heart failure (HF) remains a leading cause of morbidity and mortality globally. While the overall incidence of HF in the United States appears to be stable or declining, the incidence of heart failure with preserved ejection fraction (HFpEF) is steadily rising[1]. HFpEF now accounts for more than 50% of all HF cases. It is defined by the presence of typical heart failure symptoms and signs, a left ventricular ejection fraction (LVEF) ≥ 50%, and evidence of diastolic heart failure dysfunction or elevated cardiac filling pressures.

Despite having comparable clinical outcomes such as rates of hospitalization and mortality to heart failure with reduced ejection fraction (HFrEF), it is considered separate conditions due to their underlying pathophysiology[2]. While reduced contractility and ventricular dilation lead to HFrEF where systolic dysfunction dominates, HFpEF's primary issue lies in diastolic dysfunction that leads to elevated filling pressures from increased stiffness in left ventricle and impaired relaxation. This distinct pathophysiology involves different clinical presentation and utilization of types of therapies. For example, certain drugs such as ACE inhibitors and beta-blockers are shown to be effective in HFrEF, but benefits are minimal in HFpEF. These unique mechanisms for each disease state warrant distinct clinical approaches for HFpEF and HFrEF.

HFpEF is often underdiagnosed and undertreated and significantly contributes to healthcare resource utilization as many patients with HFpEF experience frequent hospitalizations, high rates of re-admission, and increased use of outpatient and emergency services[3]. Higher number of visits to the hospital is also related to substantial economic burden for patients.

To recognize emerging evidence, the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure introduced new pharmacologic recommendations for HFpEF, including the use of sodium-glucose cotransporter-2 inhibitors (SGLT2i), mineralocorticoid receptor antagonists (MRA), and angiotensin receptor-neprilysin inhibitors (ARNI)[3]. Initially designed to manage blood glucose in patients with type 2 diabetes mellitus (T2DM), SGLT2i have demonstrated significant cardiovascular benefits in both T2DM and non-T2DM populations, with notable benefits of reducing the risk of HF hospitalizations and cardiovascular death across the full spectrum of LVEF. As a result, SGLT2i are now recommended as first-line therapy for all HFpEF patients without contraindications[1].

MRAs including spironolactone, eplerenone, and finerenone act by blocking aldosterone-mediated sodium retention and myocardial fibrosis. These agents are particularly beneficial in reducing heart failure hospitalizations among patients with LVEF near 50%[1]. However, MRAs are associated with risks such as hyperkalemia, especially in patients with chronic kidney disease, which may require close monitoring of renal function or lead to treatment

discontinuation[5]. Additionally, spironolactone may cause gynecomastia in approximately 10% of male patients[6]. ARNIs such as sacubitril/valsartan work by combining neprilysin inhibition with angiotensin receptor blockade, thereby reducing neurohormonal activation. They are typically used in selected HFpEF patients with LVEF closer to the lower range and to further reduce the risk of HF-related hospitalizations[1]. Common adverse events associated with ARNIs include hypotension and hyperkalemia, which require careful renal monitoring of potassium levels and potential dose adjustments.

Given this evolving therapeutic landscape, we selected two groups of combination therapies, SGLT2i+MRA and SGLT2i+ARNI, for comparative evaluation based on their overlapping clinical indications and particular relevance to key subpopulations with HFpEF, especially women and patients with mildly reduced LVEF[6]. The 2023 guidelines suggest SGLT2i as foundational therapy (Class 2a) with MRAs and ARNIs holding Class 2b recommendations as adjunct therapies in similar populations including women with all ejection fractions (EF) and men with EF<55-60%[1]. These overlapping clinical indications and the absence of head-to-head comparative data on these combination therapies offer an opportunity to evaluate the clinical and economic impacts[7].

Moreover, recent meta-analyses indicate that the benefits of SGLT2i are additive when used with MRAs and ARNIs in reducing HF hospitalizations and cardiovascular death[8]. Particularly, empagliflozin has been associated with reduced discontinuation of MRAs, which further suggests a favorable profile of combination therapy. Given the high prevalence of HFpEF in women and emerging evidence of sex-specific therapeutic effects, this study addresses an evidence gap by evaluating healthcare costs and resource use among commercial and Medicare-enrolled patients with HFpEF. This study specifically compares healthcare resource utilization and costs between patients receiving SGLT2i with adjunctive ARNI versus those with adjunctive MRA therapy.

2. METHODS

2.1 STUDY DESIGN AND DATA SOURCE

Data from Merative™ MarketScan® Research (commercial and Medicare) Databases were utilized to conduct a retrospective cohort study among people with HFpEF who initiated new combination treatment with either an MRA or ARNI added to an SGLT2i. These proprietary databases compile comprehensive healthcare claims data from employer-sponsored health insurance and Medicare supplemental insurance plans in the United States. They integrate medical and prescription drug claims as well as enrollment and demographic data, making them a valuable resource for healthcare utilization (HCRU) and cost research. Specifically, for this study, we extracted all enrollment, inpatient (IP), outpatient (OP), and OP prescription drug

claim records from both databases between January 1, 2019 and December 31, 2023 (Figure 1, Appendix A).

2.2 SAMPLE SELECTION

We identified adult patients aged 18 or older with a diagnosis of HFpEF who initiated adjunct therapy with either an MRA or an ARNI following baseline treatment with SGLT2i. Eligible subjects were selected from commercial and Medicare claims databases using International Classification of Diseases, 10th Revision (ICD-10) diagnosis codes for diastolic heart failure across IP and OP settings. A comprehensive list of ICD-10 codes that include all relevant subcodes to capture all cases related to HFpEF is provided in Appendix B.

The index period was defined from January 1, 2020, to December 31, 2022, and the index date was the first prescription fill for either an MRA or ARNI during the index period. Patients were required to be diagnosed with HFpEF prior to the index date and to have at least 12 months of continuous enrollment in commercial or Medicare coverage both before and after the index date. We allowed transitions from commercial to Medicare coverage during this period. To ensure that SGLT2i use was continuously used during the study period with adjunct therapy, at least one claim for an SGLT2i in the 12 months prior to the index date and at least one additional claim in the 12 months following the index date were required. To form two distinct groups of cohorts receiving SGLT2i+MRA and SGLT2i+ARNI, patients who had overlapping use of both an MRA and an ARNI during the index period were excluded.

The final inclusion criteria were defined as (1) Age ≥ 18 years with continuous enrollment in commercial or Medicare insurance for at least 12 months before and after the index date by including possible transitions between payer types, (2) HFpEF diagnosis prior to the index date, (3) At least one OP prescription claim for either an MRA or ARNI during the index period, and (4) Ongoing use of SGLT2i therapy with at least one claim in both the pre- and post-index date. To assess healthcare resource utilization and cost outcomes, patients were followed for 12 months after the index date. Figure 2 depicts the cohort selection process.

2.3 STUDY MEASURES AND OUTCOMES

Baseline Patient Characteristics. Patients' baseline characteristics were assessed at the index date and included age, sex, index year, geographic region, Charlson Comorbidity Index (CCI) score, and the presence of key comorbidities such as diabetes mellitus (DM), coronary artery disease (CAD), chronic kidney disease (CKD), atrial fibrillation (AF), and hypertension (HTN). Health plan types (commercial or Medicare) were also recorded. HFpEF diagnoses were identified using ICD-10 codes prior to the index date, and CCI scores were calculated based on diagnosis data from the 12 months prior to the index date. Individual comorbidities were similarly identified based on the ICD-10 codes to capture each clinically relevant comorbidity related to HFpEF[2].

HCRU and Costs. Our primary outcomes of interest include HCRU and costs within the one-year period following the initiation of additional therapy with either MRA or ARNI. The HCRU analysis included several key categories of HCRU: the number of IP services, length of stay (LOS) per IP admission, number of days with emergency department (ED) services, number of OP services, and days with OP services. To define healthcare settings and service types for ED and OP/ambulatory visits, the variable "STDPLAC" was used based on specific place-of-service codes (Appendix C). However, these codes were not used to identify IP care settings because HCRU and costs for IP setting were exclusively derived from IP admission files.

Cost assessment included total one-year total healthcare costs, as well as costs stratified by care setting and service type such as IP, ED, OP, and pharmacy. Mean costs for specific subcategories such as IP, ED, OP, and pharmacy were calculated across all patients, regardless of whether they used each specific service. Also, the total costs were calculated by summing all service categories at the patient level and derived the average across all patients to provide a comprehensive view of the financial burden associated with HFpEF treatment following the initiation of additional therapy. This approach ensures that the comparison between the mean of subcategory costs and total costs is consistent, and this can avoid biases that can occur when subcategory means are calculated only among specific service users. All costs were adjusted to 2024 U.S. dollars using the medical care component of the U.S. Consumer Price Index[9].

2.4 STASTISTICAL ANALYSIS

Baseline demographics were summarized using descriptive statistics. Continuous variables, such as age, were described with mean and standard deviation, while categorical and binary variables were summarized with counts and percentages. To compare baseline characteristics between the two treatment cohorts, we used a two-sample t-tests for continuous variables such as age and chi-square tests for categorical variables such as sex, index year, health plan type, and geographic region.

In addition to p-values, we reported standardized mean differences (SMDs) to evaluate baseline comparability between the groups. While p-values report the statistical significance in observed differences, SMDs indicate the magnitude of the difference regardless of sample size, which allow them to appropriately assess baseline balance in observational studies[10-12]. With an SMD greater than 0.1 considered to indicate a meaningful imbalance, reporting both p-values and SMDs would provide insights into both statistical and clinical relevance of the differences between the two treatment groups.

Continuous HCRU outcomes such as the number of IP admissions, ED visits, OP visits, and LOS were summarized using means with SD, medians with interquartile ranges (IQR), and minimum and maximum values, as appropriate. We also reported the number and percentage of patients with at least one service use (e.g., ≥1 IP admission, ED visit, or OP service visit), and the

mean LOS per admission, the mean number of unique ED days per patient, and the mean number of days with OP services per patient were calculated.

Multivariable regression models were used to evaluate the differences in HCRU and costs between the two cohort groups. Negative binomial regression was used for count outcomes such as the number of admission or ED visits, while generalized linear models with a Gamma distribution and log link were used for cost outcomes such as IP, OP, and pharmacy costs.

Covariates included in all models were age, sex, index year (2020-2022), health plan type (commercial, Medicare), Charlson Comorbidity Index (CCI) category (1, 2, ≥3), and key comorbidities such as type 2 diabetes mellitus (T2DM), coronary artery disease (CAD), chronic kidney disease (CKD), atrial fibrillation (AF), and hypertension (HTN). All covariates were modeled as categorical variables except for age as we specifically tested whether age should be modeled as a continuous linear variable, non-linear spline, or categorical variable for the best model fit using likelihood ratio tests (LRT) and Akaike Information Criterion (AIC). Age was modeled as a linear variable for total IP admissions, LOS, and ED visits, but as a non-linear (spline) variable for OP visits. For cost outcomes, age was modeled as a spline only for IP costs, but linear for all other cost outcomes such as ED, OP, and pharmacy costs. The MRA group served as the reference group in all multivariable models, and the results are presented as incidence rate ratios (IRRs) or cost ratios with 95% confidence intervals.

To evaluate potential effect modification, we included the interaction terms for selected covariates, specifically age, sex, and CKD status, between the two treatment groups in the multivariable regression models. For each outcome, interaction terms such as treatment group x sex were added to the model along with the main effects. This allowed us to assess whether the association between the treatment group and the outcome is different in categories under the specific covariates (e.g., between males and females). The estimated coefficients and associated p-values within the adjusted models indicate how significant these interaction terms were.

Patient cohorts, baseline demographic analyses, HCRU and costs analyses were identified using SAS version 9.4 (SAS Institute, Cary, NC) and regression modeling was conducted in RStudio version 4.3.2 (Rstudio Inc., Boston, MA). All statistical analyses were performed using these platforms. This study used de-identified administrative claims data and met criteria for non-human subjects' research, as defined by the Human Subjects Division. As such, it was exempted from the Institutional Review Board (IRB) review at the University of Washington.

3. RESULTS

3.1 Baseline Patient Characteristics

After applying inclusion and exclusion criteria, we included a total of 2,128 patients diagnosed with HFpEF in the final analysis. Two mutually exclusive cohort groups with a different adjunct therapy (MRA or ARNI) following baseline SGLT2i treatment were formed: 1,418 patients in MRA group and 710 patients in ARNI group.

In the overall study population, the mean age was 67.0 years (SD=12.9), with 54.6% of patients aged ≥ 65 years. 43.0% of the cohort was females, and 55.3% was Medicare-enrolled. The most common comorbidities include HTN (89.9%) and T2DM (62.5%). When comparing the two treatment groups, the mean age was slightly lower in the ARNI group compared to the MRA group (66.1 vs. 67.5 years; p=0.032; SMD=0.10), and proportion of males was higher (64.4% vs. 53.2%; p<0.001; SMD=0.227). Differences were also observed in age group distribution (p=0.004; SMD=0.170), year of therapy initiation (p=0.020; SMD=0.132), and health plan (p=0.012; SMD=0.118). Coronary artery disease (CAD) was more common in the ARNI group (54.9% vs. 45.8%; p<0.001; SMD=0.183). All other baseline characteristics were well balanced across groups as SMDs were below 0.1 (Table 1).

3.2 Primary Outcomes

Overall, both treatment groups exhibited high HCRU during the 12-month follow-up period. Majority of patients had at least one IP admission, ED visit, or OP service (Table 2). Despite substantial use of services from both treatment groups, adjusted analysis estimated that there is lower HCRU in the ARNI group compared to the MRA group across all domains.

Inpatient (IP) Admissions. The proportion of patients having at least one IP admission was similar in both MRA and ARNI groups (79.13% vs. 79.01%). Among those with ≥1 admission, the unadjusted mean (SD) number of admissions was slightly higher in the MRA group than the ARNI group (3.1 (2.6) vs. 2.9 (2.5)), with a median (IQR) of 2.0 (1.0-4.0) in both groups. The average LOS per admission was longer in the MRA group at 20.3 (29.2) days compared to 16.9 (23.6) days in the ARNI group, with a median (IQR) of 12.0 (5.0-24.0) vs. 10.0 (5.0-20.0), respectively. In adjusted regression models, the ARNI group was associated with 9.0% fewer total IP admissions (adjusted IRR, 0.91; 95% CI, 0.842-0.982) and 20% shorter LOS (adjusted IRR, 0.80; 95% CI, 0.724-0.888) relative to the MRA group (Table 2).

Emergency Department (ED) Visits. The proportion of patients with ≥1 ED visit was slightly higher (56.5%) among patients in the MRA group compared to the ARNI group (52.4%). Among those with ≥1 ED visit, the unadjusted mean (SD) number of unique ED days was 3.5 (3.4) in the MRA group vs. 3.1 (3.0) in the ARNI group, with both groups showing the same median (IQR) of 2.0 (1.0-4.0). Adjusted analysis indicated that the ARNI group had 12% fewer ED visits than the MRA group (adjusted IRR, 0.880; 95% CI: 0.793-0.977) (Table 2).

Outpatient (OP) Visits. OP service use was nearly universal and similar in both groups, with 99.7% in the MRA group and 99.0% in the ARNI group having ≥1 OP service visit. Among these patients, the unadjusted mean (SD) number of days with OP services was 38.7 (28.9) and 34.1 (25.5), respectively, with a median (IQR) of 32.0 (19.0-51.0) days for MRA and 28.0 (16.0-46.0) days for ARNI. Adjusted analysis showed that the ARNI group had 10.7% fewer OP service days (IRR, 0.893; 95% CI: 0.837-0.953) (Table 2).

Covariate Effects and Interaction Analyses. Interaction terms were tested to assess potential effect modification between treatment groups and key covariates including age, sex, and CKD status, for each count outcome in fully adjusted count models. These covariates were selected based on their clinical relevance and statistical significance from the main regression analysis. Sex was included due to their prognostic significance in heart failure[14], while age and CKD status were included given their high prevalence and contribution to disease progression among patients with HFpEF[15,16]. From this analysis, a significant interaction was identified only between the treatment group and CKD status for ED visits (p=0.0346) which indicates that CKD status may modify the treatment effect. Consistent treatment effects were indicated as there were no significant interactions for age or sex across any of the count outcomes (Appendix D).

3.3 Secondary Outcomes

Unadjusted mean costs of total healthcare were slightly higher in the ARNI group compared to the MRA group (Table 3). The mean (95% CI) total cost was $224,038 ($201,032-$247,043) in the ARNI group and $233,568 ($214,019-$253,118) in the MRA group. In addition, IP costs ($79,245 vs. $81,733), ED costs ($103,350 vs. $110,016), and OP costs ($21,089 vs. $22,464) were all slightly lower in the ARNI group. Notably, higher OP pharmacy costs were observed in the ARNI group ($20,354 vs. $19,356) which were primarily attributable to drug cost differences as spironolactone accounts for the majority of MRA use (96.4%) (Appendix E).

In adjusted Gamma regression models with a log link, there were no statistically significant differences between the treatment groups in IP, ED, OP, and pharmacy costs (Table 3). However, across models, some patient-level covariates were independently associated with higher costs. Particularly, higher Charlson Comorbidity Index (CCI) scores, presence of comorbidities such as CAD, CKD, and AF were significantly associated with increased IP and ED costs (Appendix F).

To assess potential effect modification, interaction terms were included to assess whether the cost differences between ARNI and MRA treatments varied by sex, age, or CKD status. None of these interaction terms were statistically significant (all p>0.05) which indicates that the cost-related effects of treatments are consistent across these subgroups.

4. DISCUSSION

In this real-world retrospective analysis of patients with HFpEF treated with a combination therapy of either SGLT2i+MRA or SGLT2i+ARNI, overall, we found that both treatment groups have high HCRU, but lower HCRU was consistently demonstrated in the ARNI group in all settings across IP, ED, OP. Both unadjusted and adjusted models show these differences, and these results could be due to different patient's clinical profiles, patterns of care, and different responses to treatments' efficacy and adverse events.

HCRU. Adjusted negative binomial regression models demonstrated that there are significantly fewer IP admissions, ED visits, OP service days, and shorter average LOS in the ARNI group compared to the MRA group. This result shows that although both groups have similar rates of having at least one encounter across all healthcare settings, patients in the ARNI group may be involved with the healthcare system less frequently once they are engaged in the healthcare system. This finding aligns with clinically emerging evidence that both MRAs and ARNIs are recommended in the recent guideline for those with similar clinical characteristics such as women across the full range of EF and for men with EF<55-60%. However, MRA usage may be limited due to some concerns of distinct tolerability and adverse events such as hyperkalemia[1].

Healthcare Costs. Although the ARNI group had lower HCRU compared to the MRA group, we observed no statistically significant differences in adjusted medical costs across IP, OP, and ED services compared to the MRA group. Specifically, the ARNI group had approximately 3% lower IP costs, 6% lower ED costs, and 6% lower OP costs compared to the MRA group. These slight reductions suggest that fewer healthcare encounters translated into measurable, but not statistically significant medical spending savings. Importantly, this highlights that while pharmacy costs could be a major driver of total costs, reducing HCRU can still be meaningful savings on the medical side.

Effect Modification. We explored potential effect modification by covariates of age, sex, and CKD status across both HCRU and cost outcomes. There was only one statistically significant interaction found between CKD status and treatment group in ED visits. This suggests that patients with CKD may have different benefits from ARNI and MRA associated with ED utilization. Given that there were no other statistically significant interactions, overall treatment effects on HCRU and costs are identified to be consistent across all the covariates.

Implications. Without significant cost differences between the two treatment groups, these findings indicate that personalized treatment selection is necessary for HFpEF patients. In the real-world clinical setting, selection of MRA or ARNI in addition to the baseline treatment of SGLT2i should be carefully guided by patient-specific factors considering their renal function, the presence of CAD comorbidity, drug tolerability regarding the adverse events, and drug efficacy based on sex. While clinical trials support the additive cardiovascular benefits of

SGLT2i, MRAs, and ARNIs[17], our study is important to give insights on how combination therapy of these agents contributes to the healthcare utilization and economic implications in the case when the triple therapy is not feasible.

Moreover, less frequent visits to IP and ED might offset higher pharmacy costs incurred from the ARNI group, particularly for high-risk patients who can be hospitalized more often. Payers and providers should be aware of this cost trade-off when considering using combination therapies for HFpEF patients by evaluating the cost-effectiveness.

Limitations. This study has several limitations. As this study is based on analyzing retrospective claims data, potential residual confounding may persist. Although we adjusted for several covariates, unmeasured variables including lab values such as LVEF, blood pressure, or potassium levels were not available. Additionally, the analysis did not account for patients' disease severity, socioeconomic status, patient-reported symptoms, or clinical rationale of why a particular drug was chosen or discontinued. These unmeasured factors can cause residual confounding that may contribute to biasing the findings even after adjusting for covariates[18].

Moreover, there could be a treatment selection bias from providers choosing drugs based on patient-specific clinical characteristics such as comorbidities, adverse event history, tolerability, or patients and providers' preferences. Decisions on choosing such drug therapies were not made randomly in this observational study which might introduce systematic differences in outcomes between the two treatment groups that could be due to different baseline patient characteristics, not the treatment effect of drugs[19].

Lastly, as this study only captured data from commercial and Medicare-insured patients, these findings may not be generalizable to uninsured or Medicaid-enrolled. Also, the main purpose of claims data is for billing rather than clinical reasons which may incompletely capture full clinical history of patients as well as misclassification of diagnoses. These limitations may affect the external validity of our findings.

5. CONCLUSION

To our knowledge, this is the first study to compare HCRU and costs among patients with HFpEF treated with SGLT2i in combination with either MRAs or ARNIs since the recent updates to clinical guidelines. Our study underscores real-world insights into how adjunct therapies influence HCRU and costs with a baseline therapy of SGLT2i.

This study found that although patients in the ARNI group experienced fewer IP admissions, ED visits, and shorter LOS compared to the MRA group, these differences were found to be not statistically significant in total IP, OP, or ED costs. However, the ARNI group had notably higher pharmacy costs likely due to the higher acquisition cost of sacubitril/valsartan compared to generic MRAs.

A significant interaction between CKD status and treatment group in ED visits was found from an effect modification analysis. This may suggest that renal function may modify the relative benefits of ARNI versus MRA therapy in this population, emphasizing the significance of tailoring the treatment regimen based on comorbidities. Additionally, factors such as sex and CAD were related to lower pharmacy costs that might lead to patients' adherence to medications or providers' prescribing patterns which need to be further investigated.

These findings support the need for individualized treatment strategies to manage HFpEF. In the case when triple therapy is not feasible, understanding the proper usage of SGLT2i dual combinations can help clinicians, payers, and policymakers make informed decisions. Ultimately, optimizing treatment regimens based on not only clinical context but also costs will give valuable insights to balance patient outcomes with economic values in managing HFpEF.

6. TABLES

Table 1. Baseline Characteristics

Characteristics	Total study population (n=2,128)		p-value	Standardized mean differences (SMD)
Groups	**SGLT2i+MRA**	**SGLT2i+ARNI**		
n	1,418	710		
Age, mean (SD), years	67.5 (12.7)	66.1 (13.2)	0.032	-0.10
Age Group – n (%)			0.004	0.170
<35 years	6 (0.42)	12 (1.69)		
35-44 years	44 (3.10)	22 (3.10)		
45-54 years	178 (12.55)	101 (14.23)		
≥55 years	385 (27.15)	217 (30.56)		
≥65 years	805 (56.77)	358 (50.42)		
Sex – n (%)			<0.001	0.227
Males	755 (53.24)	457 (64.37)		
Females	663 (46.76)	253 (35.63)		
Year of Additional Therapy Initiation – n (%)			0.020	0.132
2020	164 (11.57)	56 (7.89)		
2021	361 (25.46)	202 (28.45)		
2022	893 (62.97)	452 (63.66)		
Health Plan – n (%)			0.012	0.118
Commercial	606 (42.74)	345 (48.59)		
Medicare	812 (57.26)	365 (51.41)		
Geographic Region – n (%)			0.146	0.120
Northeast	219 (15.44)	107 (15.07)		
North Central	632 (44.57)	294 (41.41)		
South	448 (31.59)	261 (36.76)		
West	116 (8.18)	46 (6.48)		
Unknown	3 (0.21)	2 (0.28)		
Charlson Comorbidity Index (CCI) – n (%)			0.436	0.058
Mean, SD	6.36 (2.75)	6.28 (2.88)		
1 – n (%)	23 (1.62)	16 (2.25)		
2 – n (%)	71 (5.01)	41 (5.77)		
≥3 – n (%)	1,324 (93.37)	653 (92.0)		
Comorbidities,[a] – n (%)				
Diabetes Mellitus (DM)	897 (63.26%)	433 (60.99%)	0.330	0.047
Coronary Artery Disease (CAD)	650 (45.84%)	390 (54.93%)	<0.001	0.183
Chronic Kidney Disease (CKD)	228 (16.08%)	113 (15.92%)	0.973	0.044
Atrial Fibrillation (AF)	605 (42.67%)	280 (39.44%)	0.168	0.066
Hypertension (HTN)	1,275 (89.92%)	638 (89.86%)	1.000	0.002

[a] *Categories are not mutually exclusive.*

Table 2. Healthcare Resource Utilization

Characteristic	Total study population (n=2,128)		
Groups	**SGLT2i+MRA**	**SGLT2i+ARNI**	**Adjusted IRR (95% CI)**
n	1,418	710	
Inpatient Admissions			
Had ≥1 admission, n (%)	1,122 (79.13%)	561 (79.01%)	
Number of admissions among patients with ≥1 admission, mean (SD)	3.1 (2.6)	2.9 (2.5)	0.909 (0.842-0.982)*
Median (IQR)	2.0 (1.0-4.0)	2.0 (1.0-4.0)	
Min	1.0	1.0	
Max	27.0	18.0	
Length of stay per admission among patients with ≥1 admission, mean (SD), days	20.3 (29.2)	16.9 (23.6)	0.802 (0.724-0.888)*
Median (IQR)	12.0 (5.0-24.0)	10.0 (5.0-20.0)	
Min	1.0	1.0	
Max	418.0	254.0	
Emergency Department Visits			
Had ≥1 visit, n (%)	801 (56.49%)	372 (52.39%)	
Number of unique days per patient among patients with ≥1 visit, mean (SD)	3.5 (3.4)	3.1 (3.0)	0.880 (0.793-0.977)*
Median (IQR)	2.0 (1.0-4.0)	2.0 (1.0-4.0)	
Min	1.0	1.0	
Max	34.0	29.0	
Outpatient Services			
Had ≥1 service, n (%)	1,414 (99.72%)	703 (99.01%)	
Days with outpatient services, among patients with ≥1 service, mean (SD)	38.7 (28.9)	34.1 (25.5)	0.893 (0.837-0.953)*
Median (IQR)	32.0 (19.0-51.0)	28.0 (16.0-46.0)	
Min	1.0	1.0	
Max	250.0	174.0	

Healthcare resource utilization was derived during the 12 months following the index date.
IQR = Interquartile Range.
IRR = Incidence Rate Ratio.
**p<0.05 indicating statistical significance based on 95% CI excluding 1.0.*
Models were adjusted for age, sex, year of initiating an adjunct therapy, health plan, region, CCI scores, and comorbidities unless otherwise noted. Adjusted IRRs were estimated using negative binomial regression to account for over-dispersed count data; IRRs<1 indicate lower expected event rates and IRRs>1 indicate higher expected event rates in the ARNI group vs. MRA group.

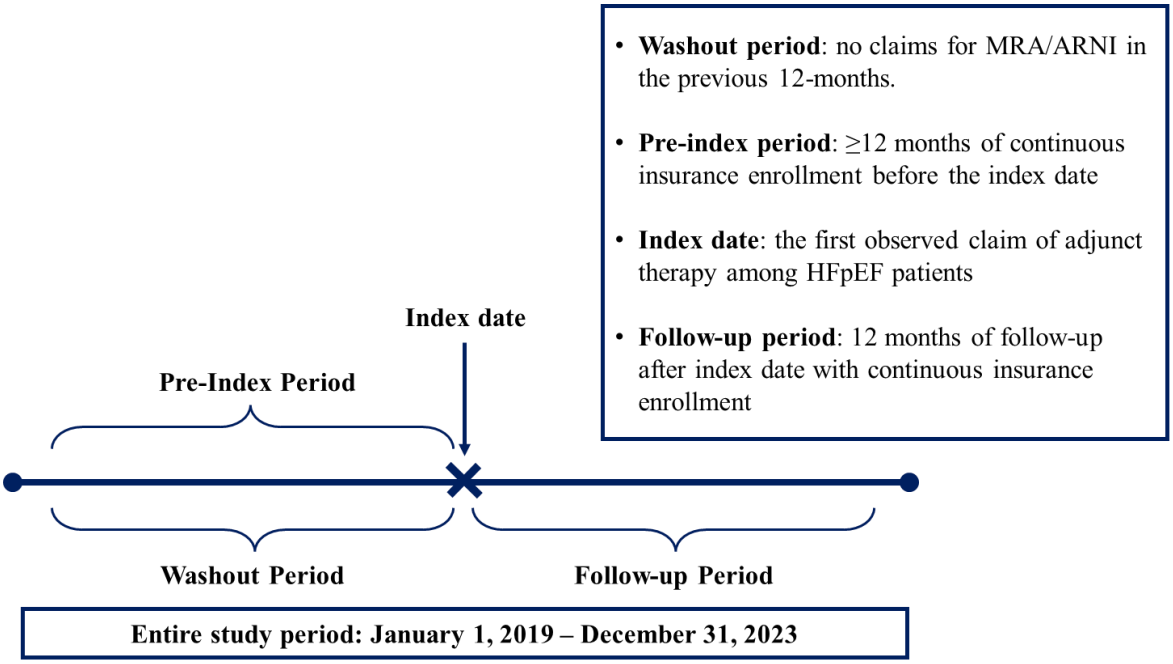
Table 3. Healthcare Costs

Characteristic	Total study population (n=2,128)		
Groups	**SGLT2i+MRA**	**SGLT2i+ARNI**	**Adjusted Cost Ratio**
n	1,418	710	
Medical Costs			
Total Inpatient Costs mean (95% CI)	$81,733 ($73,591-$89,876)	$79,245 ($68,551-$89,939)	0.985 (0.887-1.093)
Total ED Costs mean (95% CI)	$110,016 ($98,862-$121,169)	$103,350 ($90,321-$116,379)	1.036 (0.955-1.123)
Total Outpatient Costs mean (95% CI)	$22,464 ($20,208-$24,719)	$21,089 ($18,097-$24,080)	0.996 (0.899-1.102)
Pharmacy Costs			
Total Pharmacy Costs mean (95% CI)	$19,356 ($17,358-$21,353)	$20,354 ($18,456-$22,252)	1.101 (0.949-1.278)
Mean Total Costs (95% CI)	**$233,568 ($214,019-$253,118)**	**$224,038 ($201,032-$247,043)**	

Costs were identified using the payment variable for ED and OP costs and total payment variable for IP costs. Healthcare costs were derived during the 12 months following the index date.
Models were adjusted for age, sex, year of initiating an additional therapy, health plan, region, CCI scores, and comorbidities unless otherwise noted. Adjusted cost ratios were estimated using gamma regression with a log link to account for skewed cost data; values<1 indicate lower expected costs and values>1 indicate higher expected costs in the ARNI group vs. MRA group.
The observed differences in pharmacy costs may reflect drug acquisition costs, as the average wholesale price (AWP) per unit for sacubitril/valsartan (Entresto) was approximately $14.10, compared to $0.82 for generic spironolactone[20-21].

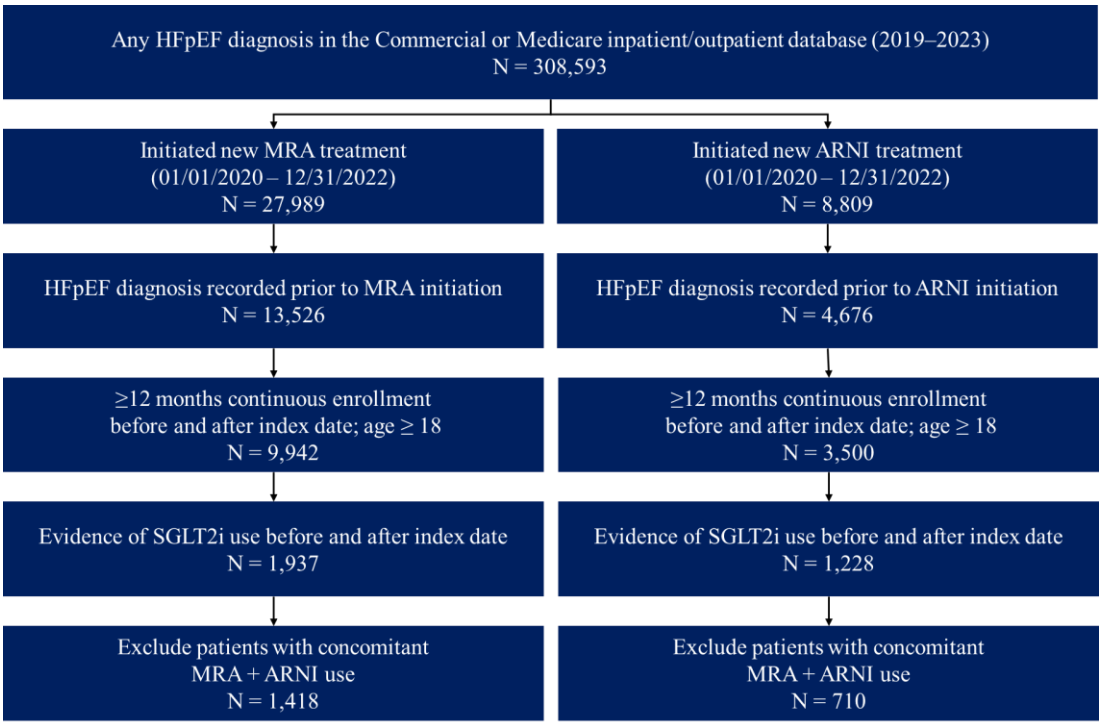
7. FIGURES

Figure 1: Study Design



MRA: mineralocorticoid receptor antagonists; ARNI: angiotensin receptor-neprilysin inhibitor

Figure 2: Sample Selection Process



8. APPENDIX

Appendix A – MarketScan Tables

Abbreviation	Data
I*	Inpatient Admissions*
F	Facility Header
S*	Inpatient Services*
O*	Outpatient Services*
D*	Outpatient Drug Claims*
A*	Annual Summary Enrollment*
T	Data Enrollment
R*	Redbook*

**Data used in our study*

Appendix B – ICD Diagnosis Codes

Code	Definition
I50.30	Unspecified diastolic (congestive) heart failure
I50.31	Acute diastolic (congestive) heart failure
I50.32	Chronic diastolic (congestive) heart failure
I50.33	Acute on chronic diastolic (congestive) heart failure

Appendix C – Descriptions of Healthcare Setting

Claim type	Definition
Emergency Department	1. STDPLAC = 23 (emergency room – hospital) or SVCSCAT ending with "20" (emergency services)

Outpatient/Ambulatory Setting (Exclude SVCSCAT not ending with "20" (emergency services)	
Office visit	1. STDPLAC = 11 (office), 18 (place of employment), 49 (independent clinic), 50 (federally qualified health center), 71 (state or local public health clinic), 72 (rural health clinic), 95 (outpatient not elsewhere classified), 65 (ESRD Treatment Facility) or 99 (other)
Hospital outpatient department	1. STDPLAC = 19 or 22 (on-campus of off-campus outpatient hospital)
Urgent care center	1. STDPLAC = 20 (urgent care center), 41 (ambulance-land), 42 (ambulance-air or water)
Retail clinic	1. STDPLAC = 17 (walk-in retail clinic)
Outpatient surgery	1. STDPLAC = 11 (office), 19 or 22 (on-campus or off-campus outpatient hospital), or 24 (ambulatory surgery center)
Mobile unit	1. STDPLAC = 15
Home visit	1. STDPLAC = 12 (patient home)
Behavioral health care	1. STDPLAC = 53 (community mental health center), 62 (comprehensive outpatient rehabilitation facility), 57 (non-residential substance abuse treatment facility), 55 (residential substance abuse treatment facility), 56 (psychiatric residential treatment center)

Appendix D – Interaction Effects from Adjusted Negative Binomial Models for Count Outcomes

Interaction Term	Outcome	p-value	Interpretation
Treatment x CKD	ED visits	0.0346	Significant
Treatment x Age	All outcomes	>0.05	Not significant
Treatment x Sex	All outcomes	>0.05	Not significant

CKD: Chronic Kidney Disease

Appendix E – Distribution of MRA Use by Generic Drug

Generic Drug Name	Number of Patients, n (%) (N=1,418)
Spironolactone	1367 (96.4%)
Eplerenone	30 (2.1%)
Finerenone	21 (1.5%)

Appendix F – Patient-Level Covariates Associated with Healthcare Costs in Adjusted Gamma Regression Models

Covariate	Adjusted Cost Ratios	95% CI
IP Cost		
Charlson Comorbidity Index (CCI_cat)	1.39	1.09-1.76
Coronary Artery Disease (has_CAD_flag)	1.24	1.09-1.41
Chronic Kidney Disease (has_CKD_flag)	1.23	1.05-1.45
Atrial Fibrillation (has_AF_flag)	1.25	1.10-1.42
ED Cost		
Charlson Comorbidity Index (CCI_cat)	1.67	1.35-2.06
Coronary Artery Disease (has_CAD_flag)	1.13	1.01-1.26
Chronic Kidney Disease (has_CKD_flag)	1.29	1.12-1.50
Atrial Fibrillation (has_AF_flag)	1.22	1.09-1.38

CCI_cat: Charlson Comorbidity Index, modeled as a categorical variable representing comorbidity burden (e.g., 1,2, ≥3)
has_CAD_flag, has_CKD_flag, has_AF_flag: binary indicator variables representing the presence (1) or absence (0) of coronary artery disease (CAD), chronic kidney disease (CKD), and atrial fibrillation (AF), respectively.

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