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Research Article

Sacubitril Valsartan Versus Mineralocorticoid Receptor Antagonists for Heart Failure Readmission Risk Across all Subtypes

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Abstract

Background: Heart failure (HF) is classified as HFrEF, HFmrEF, and HFpEF. Sacubitril/valsartan improves outcomes in HFrEF, but benefits in HFmrEF and HFpEF are less clear. MRAs reduce mortality in HFrEF and hospitalizations in HFpEF. Direct comparisons across HF subtypes, especially HFmrEF, are limited. **Goal:** To compare sacubitril/valsartan (ARNI) based therapy, MRA based therapy, and ARNI plus MRA combination therapy in HFrEF, HFmrEF, and HFpEF, specifically evaluating their association with short term all cause readmission at 7, 15, and 30 days after discharge. This analysis was designed to assess readmission risk alone and does not evaluate mortality or symptom based outcomes. Because all patients also received background therapy with an ACE inhibitor, angiotensin receptor blocker, or beta blocker, the ARNI and MRA groups are best understood as ARNI based and MRA based regimens rather than true monotherapy. **Methods:** Retrospective analysis of 23,649 adults with newly diagnosed HF from the HCA Healthcare national database (190 hospitals, ~2,400 ambulatory sites). Patients were aged 30 to 60 years, representing a comparatively younger heart failure population than most national registries, in which average age at hospitalization exceeds 70 years. Patients were stratified by EF phenotype and grouped as MRA only, ARNI only, or combination therapy; prior outpatient use was exclusionary. Readmission risks were analyzed at 7, 15, and 30 days, accounting for race and comorbidities. **Baseline Characteristics:** The cohort was 70.1% male, 54.2% White, 33.0% Black. Comorbidities included hypertension (65.2%), diabetes (26.3%), and CKD (17.7%). Most had HFrEF (68.3%), followed by HFmrEF (17.4%) and HFpEF (14.4%). MRA monotherapy was most frequent (64.1%). Among patients, 4,164 received ARNI, 15,162 MRA, and 4,323 combination therapy. **Results:** In HFrEF, MRA based therapy increased readmission odds compared with combination therapy at 7 days (OR 1.24), 15 days (OR 1.25), and 30 days (OR 1.34). ARNI based therapy increased 30-day readmissions compared with MRA based therapy in HFrEF (OR 1.19) and HFpEF (OR 1.60). CKD increased 15- and 30-day readmissions in HFrEF. In HFpEF, African American race was linked to lower 15- and 30-day readmissions, a finding discussed further in the Discussion as a possible reflection of differential outcome ascertainment rather than a true protective effect.

Abbreviations: HF – Heart Failure; HFrEF – Heart Failure with Reduced Ejection Fraction; HFmrEF – Heart Failure with Mildly Reduced Ejection Fraction; HFpEF – Heart Failure with Preserved Ejection Fraction; ARNI – Angiotensin Receptor-Neprilysin Inhibitor; MRA – Mineralocorticoid Receptor Antagonist; GDMT – Guideline-Directed Medical Therapy; EF – Ejection Fraction; LVEF – Left Ventricular Ejection Fraction; ACEi – Angiotensin-Converting Enzyme Inhibitor; ARB – Angiotensin Receptor Blocker; BB – Beta-Blocker; CKD – Chronic Kidney Disease; HTN – Hypertension; DM – Diabetes Mellitus; SGLT2 – Sodium-Glucose Cotransporter-2; NYHA – New York Heart Association; RCT – Randomized Controlled Trial; OR – Odds Ratio; CI – Confidence Interval ; HR – Hazard Ratio; eGFR – Estimated Glomerular Filtration Rate; RASI – Renin-Angiotensin System Inhibitor ; ESC – European Society of Cardiology; AHA – American Heart Association; ACC – American College of Cardiology; HFSA – Heart Failure Society of America; KDIGO – Kidney Disease: Improving Global Outcomes; PPCM – Peripartum Cardiomyopathy; ECHO – Echocardiogram; HER2 – Human Epidermal Growth Factor Receptor 2; Rehospitalization – used synonymously with Readmission throughout the manuscript

Discussion

Overview and Context of this Study

The present investigation was conceived not as a challenge to existing guideline-directed medical therapy (GDMT) frameworks, but rather as a deliberate effort to capture a contemporaneous, real-world snapshot of how heart failure (HF) management is being implemented across a large and geographically diverse clinical landscape in the United States. Heart failure remains one of the most prevalent and resource-intensive cardiovascular conditions, affecting approximately 6.7 million Americans and accounting for over one million hospitalizations annually [1]. Its spectrum encompasses HF with reduced ejection fraction (HFrEF, EF ≤40%), HF with mildly reduced ejection fraction (HFmrEF, EF 41–49%), and HF with preserved ejection fraction (HFpEF, EF ≥50%). Each phenotype demands nuanced, phenotype-specific therapeutic strategies that continue to evolve [3].

The landmark trials that informed the 2022 AHA/ACC/HFSA Heart Failure Guidelines: including PARADIGM-HF, PARAGON-HF, RALES, and TOPCAT all have collectively shaped our understanding of neurohormonal modulation across the HF spectrum [3]. PARADIGM-HF demonstrated that sacubitril/valsartan (ARNI) significantly reduced the composite of cardiovascular death and HF hospitalization by 20% compared to enalapril in patients with HFrEF, establishing it as a cornerstone of modern quadruple therapy [4]. PARAGON-HF subsequently explored ARNI in HFpEF and, while it narrowly missed its primary endpoint (rate ratio 0.87; 95% CI 0.75–1.01; p=0.059), it generated hypothesis-generating signals, particularly among patients with lower-range preserved EF, that continue to inform clinical practice and ongoing research [5]. Similarly, RALES established the prognostic benefit of spironolactone in HFrEF, and TOPCAT, despite its primary endpoint neutrality, offered region-specific insight into MRA utility in HFpEF [6].

Despite this robust evidence base, a persistent and clinically meaningful gap exists between what trials demonstrate under highly controlled conditions and what transpires in the heterogeneous, real-world clinical environment. It was precisely this gap that motivated the present study. Our primary objective was to evaluate and compare the relative impact of three distinct therapeutic strategies—ARNI monotherapy, MRA monotherapy, and combined ARNI + MRA therapy (each administered alongside one or more accessory medications including ACE inhibitors, beta-blockers, or ARBs)—on 7-day, 15-day, and 30-day all-cause readmission rates across the three HF phenotypes. By doing so, we hoped to add a layer of real-world interpretive value to the existing evidence and to identify patterns that may warrant further, more granular prospective investigation.

Study Population: Demographics, Comorbidities, and Representativeness

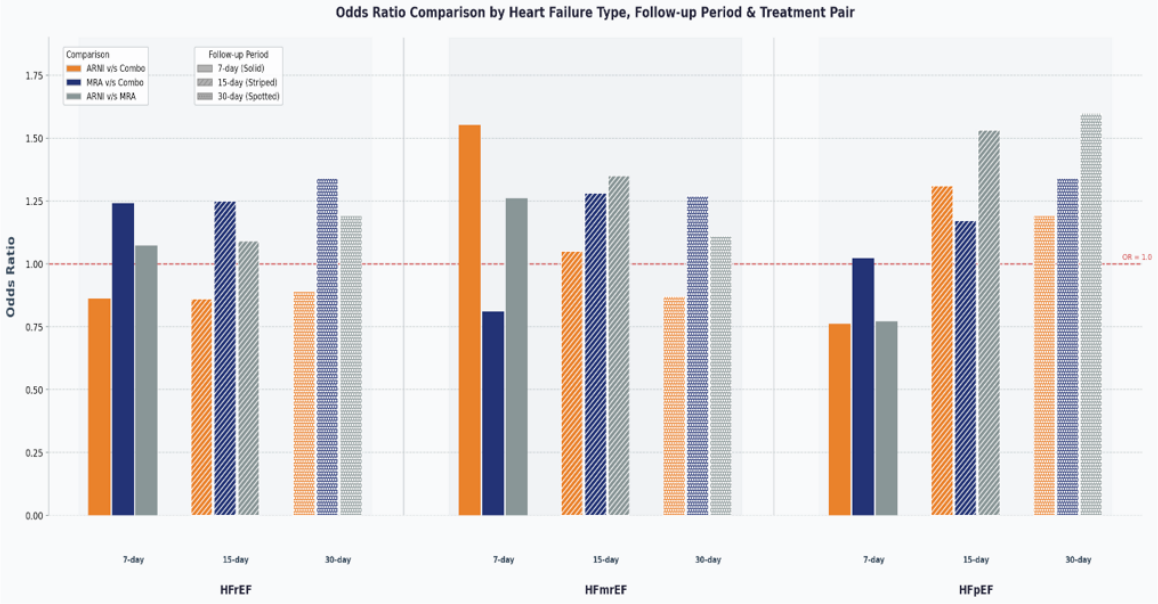
This retrospective secondary analysis drew upon de-identified patient data from the HCA Healthcare national database, spanning 190 hospitals and approximately 2,400 ambulatory care sites across the continental United States; a network that collectively represents one of the largest healthcare delivery systems in the country [8]. The resulting cohort of 23,649 adults with newly diagnosed heart failure offers a degree of geographic, racial, and institutional diversity that meaningfully strengthens the generalizability of our findings, both across clinical practice environments and across patient populations that are frequently underrepresented in classical RCT settings.

Regarding gender distribution, the cohort was predominantly male (70.1%), which is broadly consistent with existing epidemiologic data demonstrating a modestly higher incidence of HFrEF in men, though HFpEF tends to be more prevalent among women [1]. This gender imbalance is an acknowledged limitation of the present dataset. Women have historically been underenrolled in cardiovascular trials, and their systemic underrepresentation in observational registries may introduce a degree of gender-related selection bias. We therefore acknowledge that the findings of this study may not be fully generalizable to female patients, particularly in the context of HFpEF, where sex-based differences in cardiac physiology, comorbidity burden, and treatment response are clinically relevant [9].

From a racial and ethnic standpoint, the cohort comprised 54.2% White, 33.0% Black, and 12.8% patients of other racial backgrounds. This racial composition is notably more diverse than that observed in many pivotal RCTs, which have historically drawn heavily from predominantly White, European cohorts [4]. The inclusion of a substantial proportion of Black patients is particularly meaningful given well-established racial disparities in HF incidence, management patterns, pharmacogenomic responses, and outcomes [3]. We note, however, that our dataset did not allow for granular subclassification by Hispanic ethnicity or other minority groups, which remains a limitation. Additionally, detailed longitudinal mortality tracking was not feasible in this study. Because our data were derived from retrospective encounter-level records, it was not reliably possible to ascertain post-discharge mortality for patients who did not return to an HCA Healthcare facility. This challenge is not unique to our study; it reflects a broader and well-recognized structural limitation of administrative hospital datasets, wherein follow-up is contingent upon re-presentation to the same system rather than sustained outpatient surveillance. We respectfully acknowledge that this may in part reflect administrative and systems-level gaps in post-discharge patient tracking, an area that merits targeted quality improvement effort. For clarity, the mortality figure noted in (Table 1 and Graph 1), 0.3 percent, reflects only in hospital and in network deaths identified incidentally during data capture. It was not designed or intended to serve as a formal outcome measure in this study, which focuses specifically on short term all cause readmission.

Class	**Variable**	**Total, n (Percentage, %)**
Gender	Female	7079 (29.9%)
	Male	16570 (70.1%)
Race/ Ethnic origin	African American	7802 (33.0%)
	Other	3038 (12.8%)
	White	12809 (54.2%)
Mortality		65 (0.3%)
Co-Morbidities	Hypertension	15413 (65.2%)
	Diabetes	6218 (26.3%)
	Chronic Kidney Disease	4185 (17.7%)
Other Drug/Medication Use	ARB use	5492 (23.2%)
	Beta Blocker use	8105 (34.3%)
	ACE use	8734 (36.9%)
Readmission Rates	7-Day	751 (3.2%)
	15-Day	1344 (5.7%)
	30-Day	2095 (8.9%)
Study Variable Medications	ARNI only used	4164 (17.6%)
	Combination therapy used	4323 (18.3%)
	MRA only used	15162 (64.1%)
ECHO	HFmrEF	4106 (17.4%)
	HFpEF	3398 (14.4%)
	HFrEF	16145 (68.3%)

Table 1: Study Population Demographics.



Graph 1: Results of logistic regression analysis.

With respect to comorbidity burden, 65.2% of patients carried a diagnosis of hypertension (HTN), 26.3% had diabetes mellitus (DM), and 17.7% were identified as having chronic kidney disease (CKD) of any stage. It is critical to note that these comorbidities were not mutually exclusive in our dataset; indeed, a substantial proportion of patients likely harbored two or all three of these conditions simultaneously. The overlap among HTN, DM, and CKD is well-recognized and carries profound implications for cardiovascular risk, GDMT selection, and electrolyte management, particularly as it relates to tolerability of MRA therapy and the emerging role of SGLT2 inhibitors [10]. We were unfortunately unable to quantify the precise degree of comorbidity co-occurrence at the individual patient level due to the de-identified nature of the data, which represents a meaningful analytical constraint. The cardiorenal dimension of this comorbidity burden will be revisited in greater detail in a subsequent section of this discussion.

All patients in this cohort were identified as being on one or more accessory cardiovascular medications at discharge—specifically ACE inhibitors, beta-blockers, or ARBs—attributable in large part to the prevailing comorbidity landscape. These agents were not the primary study exposures but served as background therapy that contextualizes the primary treatment comparisons. A notable and significant limitation of the current dataset is the absence of data on SGLT2 inhibitor use, either prior to or upon hospital discharge. Given the 2022 AHA/ACC/HFSA guideline's Class I recommendation for SGLT2 inhibitors as a component of quadruple GDMT in HFrEF, and Class IIa recommendation in HFpEF and HFmrEF; the inability to account for this therapeutic class represents an important confounding gap [2]. We cannot exclude the possibility that differential SGLT2 inhibitor use across treatment groups may have influenced readmission outcomes, and this limitation should be borne in mind when interpreting the results. For this reason, our findings are best framed as a comparison of two and three drug regimens within guideline directed medical therapy rather than a full evaluation of comprehensive four drug therapy, and any difference in SGLT2 inhibitor use between the treatment groups should be considered a possible contributor to the associations we observed.

Three primary exposure groups were defined for analysis. The first comprised patients discharged on ARNI (sacubitril/valsartan) in combination with one or more of the aforementioned accessory medications. The second comprised patients discharged on MRA therapy (spironolactone or eplerenone) with similar accessory co-medication. The third—and guideline-aligned—group comprised patients discharged on the combination of ARNI + MRA, again alongside at least one accessory agent. These groupings allowed for a structured, three-way comparative analysis that mirrors real-world prescribing archetypes. Because every patient in this cohort also received at least one background medication such as an ACE inhibitor, angiotensin receptor blocker, or beta blocker, the terms ARNI monotherapy and MRA monotherapy are used throughout this manuscript to describe ARNI based and MRA based regimens

rather than true monotherapy, and each reported odds ratio specifies its comparator group explicitly to avoid ambiguity.

Finally, echocardiographic left ventricular ejection fraction (LVEF) data served as the basis for HF phenotypic classification. Patients with LVEF ≤40% were classified as HFrEF, those with LVEF 41–49% as HFmrEF, and those with LVEF ≥50% as HFpEF, in accordance with the 2022 AHA/ACC/HFSA and 2021 ESC HF guideline definitions [2]. The distribution within our cohort—HFrEF 68.3% (n=16,145), HFmrEF 17.4% (n=4,106), and HFpEF 14.4% (n=3,398)—is broadly consistent with population-level HF registries, with HFrEF predictably representing the largest phenotypic group given the clinical and symptomatic criteria for acute hospitalization [1]. This EF-stratified design constitutes one of the principal strengths of the study, allowing phenotype-specific inference rather than a single, pooled analysis that would obscure clinically important heterogeneity.

Study Design, Inclusion Criteria, and Important Caveats

This study included adults aged 30 to 60 years who were admitted to HCA Healthcare facilities with a newly diagnosed episode of acute heart failure in exacerbation, subsequently classified by echocardiographic LVEF findings. Older adults represent a considerable proportion of the overall heart failure population who frequently carry greater comorbidity burden, frailty, and medication intolerance. As a result, limiting the cohort to patients aged 30 to 60 years may reduce the generalizability of these findings to elderly HF populations. This limitation is particularly relevant given that advancing age is independently associated with increased readmission risk and a higher prevalence of HFpEF driven by age-related diastolic dysfunction, myocardial stiffening, and multimorbidity [2]. This consideration is especially relevant for HFpEF, which is predominantly a condition of older adults, and we encourage readers to view our HFpEF findings as reflective of a younger and likely less representative subset of that phenotype. Data were collected across a four-year period spanning 2020 through 2024. Inclusion criteria required a confirmed HF diagnosis of any EF subtype, treatment with sacubitril/valsartan and/or an MRA during the index hospitalization, and the absence of prior outpatient use of these agents, ensuring that observed treatment associations were not confounded by pre-existing medication exposures or established therapeutic responses. Patients were excluded if their HF did not meet criteria for one of the three recognized EF phenotypes, if other HF-specific therapies constituted the primary treatment approach, or if they were immunocompromised, pregnant, or carrying advanced malignancies. Given the retrospective observational nature of this analysis, this study was designed to identify associations between discharge medication strategy and readmission outcomes instead of establishing direct causal relationships [12].

Several important caveats deserve transparent acknowledgment here. First, by excluding pregnant women, this analysis is unable to speak to pregnancy-associated cardiomyopathy (PPCM), a distinct and clinically important HF etiology with unique pathophysiology, natural history, and therapeutic implications [13]. PPCM, which can present with severely reduced EF and disproportionately affects younger women and those of African descent, may exhibit different treatment responsiveness to ARNI and MRA therapies: an area of growing clinical interest that our dataset does not address.

Second, the exclusion of patients with a prior diagnosis of heart failure was deliberately implemented to ensure that the primary exposure to the medication at discharge, reflected de novo treatment initiation rather than a continuation or modification of an existing regimen. Patients with prior HF diagnoses would likely already be on established GDMT, and any observed readmission pattern would be confounded by their historical therapeutic trajectory, including prior titration, prior decompensation events, and medication-specific tolerance developed over time. While this exclusion strengthens the internal validity of the primary exposure-outcome relationship, it simultaneously reduces the real-world representativeness of our findings in the broader, established HF population. Additionally, treatment assignment was not randomized and likely reflected clinician judgment regarding hemodynamic stability, renal function, electrolyte risk, and overall patient complexity. Patients receiving MRA monotherapy may have differed systematically from those receiving combination therapy at baseline.

Third, the exclusion of immunocompromised patients and those with advanced malignancies, while methodologically appropriate to reduce outcome heterogeneity, introduces a meaningful boundary on the applicability of our findings. Oncology-related cardiomyopathies represent an increasingly prevalent and clinically complex intersection of cardiovascular and oncologic medicine. Cardiotoxic agents known to cause HF include anthracyclines such as doxorubicin and epirubicin, anti-HER2 therapies such as trastuzumab and pertuzumab, immune checkpoint inhibitors, tyrosine kinase inhibitors, fluoropyrimidines, and proteasome inhibitors such as bortezomib [14]. Additionally, direct cardiac involvement from hematologic malignancies such as lymphoma, or metastatic disease from solid tumors, may produce HF phenotypes with distinct hemodynamic, structural, and pharmacological characteristics. By excluding these patients, our analysis cannot speak to the growing field of cardio-oncology: a recognized area of clinical priority in the 2022 AHA/ACC/HFSA guidelines [3]. Future studies should specifically address GDMT tolerability and outcomes in this high-risk, rapidly growing population.

Several clinically important variables were not available within the dataset, including SGLT2 inhibitor use, NYHA functional class, natriuretic peptide levels, medication dosing and titration, outpatient follow-up adherence, and socioeconomic determinants of health. These unmeasured factors may have influenced readmission risk independently of the medication strategy analyzed and represent an important limitation of the present study. These methodological decisions improved internal consistency and exposure characterization but necessarily limited the external generalizability of the findings to broader real world heart failure populations [15].

Analytical Approach and Methodological Considerations

Following EF-based phenotypic classification, patients were further stratified by their medication regimen at discharge into one of three primary exposure groups: ARNI monotherapy (with accessory medication), MRA monotherapy (with accessory medication), or combination ARNI + MRA therapy (with accessory medication). From these three groups, three binary comparative pairs were constructed: (1) ARNI vs. ARNI + MRA; (2) MRA vs. ARNI + MRA; and (3) ARNI vs. MRA. Each comparison was then assessed against three outcome time windows—7-day, 15-day, and 30-day all-cause readmission—using multivariable logistic regression adjusted for available demographic and comorbidity covariates, with results expressed as odds ratios (OR) with 95% confidence intervals (CI) and corresponding p-values.

Although multivariable adjustment was performed, the administrative nature of the dataset limited the availability of several clinically important predictors of readmission, including medication dosing and titration, NYHA functional class, natriuretic peptide levels, outpatient follow-up adherence, and SGLT2 inhibitor use. Residual confounding from unmeasured variables remains possible. The analysis also could not account for provider-level prescribing behavior, regional practice variation, discharge planning quality, outpatient healthcare access, or differences in post-discharge follow-up, all of which may substantially influence readmission risk in patients with heart failure.

It is important to acknowledge that readmission reason data were limited by the de-identification and data collection protocols employed by the HCA Healthcare system, which precluded a granular, cause-specific analysis of rehospitalization. Furthermore, because the dataset was encounter-based and limited to HCA Healthcare facilities, readmissions or deaths occurring outside the HCA network may not have been fully captured, potentially leading to underestimation of outcome events. This form of ascertainment bias would be expected to lower our observed readmission counts more in groups with greater reliance on emergency or out of network care, and this possibility should be kept in mind when interpreting subgroup differences, particularly those related to race, which are discussed further below. This limitation is particularly relevant in a comorbidity-heavy cohort, where readmissions for metabolic disturbances, infectious complications, or renal deterioration may be disproportionately represented. As such, all readmission outcomes in this study represent all cause readmissions rather than HF-specific rehospitalizations, meaning that admissions related to infection, renal dysfunction, electrolyte abnormalities, medication-related complications, or unrelated medical conditions were analyzed alongside HF-related events. This distinction may minimize the specificity of the findings and lessen the direct HF-related outcome signal. Additionally, the present analysis was limited to short-term readmission intervals of 7, 15, and 30 days and therefore does not capture longer-term outcomes such as mortality, sustained GDMT adherence, progressive renal dysfunction, or recurrent hospitalization beyond the early post-discharge period.

All patient data employed in this analysis were fully de-identified at the point of extraction in accordance with HCA Healthcare's institutional data governance policies and compliant with applicable federal regulations governing the secondary use of protected health information. The de-identified nature of the dataset precluded the need for individual patient consent while ensuring full ethical compliance with research standards. We are grateful to HCA Healthcare for facilitating access to this large and nationally representative dataset.

Interpretation of Key Findings

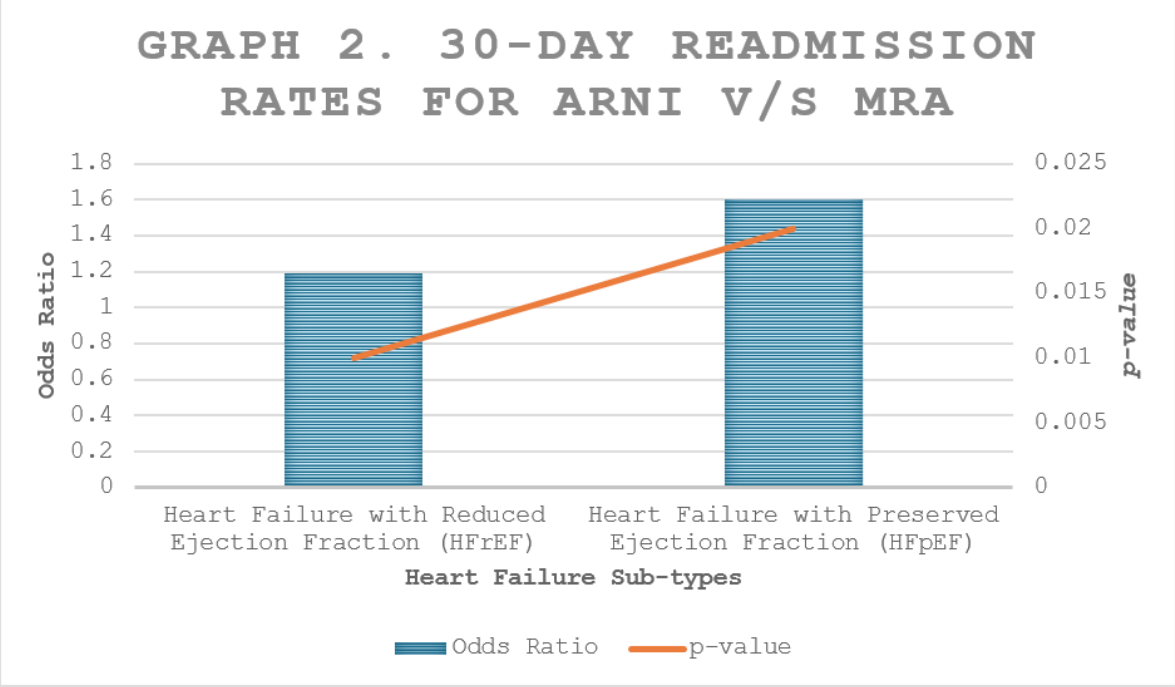
Combination GDMT vs. Monotherapy: Reinforcing the Case for Comprehensive Treatment

Perhaps the most clinically salient finding of this study is the consistent and statistically significant association between MRA monotherapy and higher all-cause readmission rates in HFrEF compared to combination ARNI + MRA therapy across all three-time windows: 7-day (OR 1.24; 95% CI 1.004–1.543; p=0.04), 15-day (OR 1.25; 95% CI 1.06–1.47; p<0.001), and 30-day (OR 1.34; 95% CI 1.17–1.53; p<0.0001). Similarly, ARNI monotherapy in HFrEF was associated with significantly higher 30-day readmission rates compared to MRA alone (OR 1.19; 95% CI 1.03–1.37; p=0.01), and in HFpEF (OR 1.60; 95% CI 1.07–2.39; p=0.02). These findings collectively reinforce a central tenet of the 2022 AHA/ACC/HFSA guidelines: that in eligible patients, comprehensive multidrug GDMT is superior to minimalistic or monotherapy-based approaches [3]. The guidelines explicitly recommend that patients with HFrEF and NYHA Class II–III symptoms be discharged on maximally tolerated GDMT, ideally encompassing all four foundational drug classes (ARNI, beta-blocker, MRA, and SGLT2 inhibitor) rather

than stepwise sequential introduction of individual agents [3]. Our real-world data provide independent, large-cohort empirical support for this paradigm, suggesting that clinicians who defer combination therapy at discharge—whether due to concerns about hemodynamic tolerability, electrolyte disturbances, renal function, or medication burden—may inadvertently expose their patients to elevated short-term readmission risk. We intend this as an association rather than a causal claim, since treatment assignment in this retrospective cohort was not randomized and likely reflected clinician judgment about individual patient suitability for combination therapy (Table 2 and Graph 2).

Heart Failure	Concordance	Readmission	Medication	ODDS ratio	p-value	Confidence interval [L.L, U.L]
HFrEF (n=16145)	0.53	7-day	ARNI v/s MRA +ARNI	0.86	0.28	[0.66, 1.13]
			MRA v/s MRA+ARNI	**1.24**	**0.04**	**[1.004, 1.543]**
			ARNI v/s MRA	1.07	0.52	[0.85, 1.35]
	0.54	15-day	ARNI v/s MRA +ARNI	0.86	0.17	[0.70, 1.06]
			MRA v/s MRA+ARNI	**1.25**	**0**	**[1.06, 1.47]**
			ARNI v/s MRA	1.09	0.33	[0.91, 1.29]
	0.54	30-day	ARNI v/s MRA +ARNI	0.89	0.16	[0.75, 1.04]
			MRA v/s MRA+ARNI	**1.34**	**<0.0001**	**[1.17, 1.53]**
			ARNI v/s MRA	**1.19**	**0.01**	**[1.03, 1.37]**
HFmrEF (n=4106)	0.54	7-day	ARNI v/s MRA +ARNI	1.55	0.14	[0.86, 2.80]
			MRA v/s MRA+ARNI	0.81	0.41	[0.48, 1.35]
			ARNI v/s MRA	1.26	0.3	[0.81, 1.96]
	0.56	15-day	ARNI v/s MRA +ARNI	1.05	0.8	[0.70, 1.58]
			MRA v/s MRA+ARNI	1.28	0.15	[0.91, 1.80]
			ARNI v/s MRA	1.35	0.08	[0.96, 1.88]
	0.54	30-day	ARNI v/s MRA +ARNI	0.87	0.41	[0.62, 1.21]
			MRA v/s MRA+ARNI	1.27	0.45	[0.98, 1.66]
			ARNI v/s MRA	1.11	0.66	[0.84, 1.47]
HFpEF (n=3398)	0.59	7-day	ARNI v/s MRA +ARNI	0.76	0.65	[0.22, 2.54]
			MRA v/s MRA+ARNI	1.02	0.55	[0.41, 2.56]
			ARNI v/s MRA	0.77	0.95	[0.33, 1.78]
	0.59	15-day	ARNI v/s MRA +ARNI	1.31	0.5	[0.59, 2.89]
			MRA v/s MRA+ARNI	1.17	0.64	[0.60, 2.26]
			ARNI v/s MRA	1.53	0.08	[0.94, 2.49]
	0.57	30-day	ARNI v/s MRA +ARNI	1.19	0.58	[0.63, 2.25]
			MRA v/s MRA+ARNI	1.34	0.26	[0.79, 2.26]
			ARNI v/s MRA	**1.6**	**0.02**	**[1.07, 2.39]**

Table 2: Primary Results for Readmission rates across Heart Failure phenotypes comparing various drugs on discharge.



Graph 2: 30-day Readmission rates for ARNI use v/s MRA use upon discharge.

The RALES Trial in Context: When Real-World Data Diverge from Landmark RCT Evidence

The finding that MRA monotherapy (with accessory medications including ACEi/ ARBs/ BB for other co-morbid diseases including but not limited to hypertension) was associated with worsened readmission odds across all time horizons in HFrEF stands in apparent contrast to the foundational evidence from the RALES trial, which demonstrated that spironolactone 25 mg daily, added to standard therapy including ACE inhibitors and loop diuretics, reduced all-cause mortality by 30% (relative risk 0.70; 95% CI 0.60–0.82; $p<0.001$) and significantly reduced heart failure hospitalization rates in patients with severe HFrEF (LVEF ≤35%) [6]. This divergence between our observational findings and the RALES RCT results is, in our view, not contradictory but rather reflective of the fundamental difference in perspective in different regional healthcare system variations and between highly controlled trial conditions and the messier reality of clinical practice.

RALES enrolled 1,663 carefully selected, protocol-adherent patients under closely monitored conditions with supervised medication titration, whereas our study captures the cumulative influence of real-world variables that trials are designed to eliminate: medication non-adherence, variable titration practices, unrecognized hyperkalemia or renal insufficiency precluding full GDMT implementation, concomitant diuretic overuse, dietary sodium non-compliance, and undocumented intercurrent illness. Furthermore, patients receiving MRA monotherapy in our cohort may intrinsically represent a subgroup with greater clinical complexity, those deemed unsuitable for ARNI due to hemodynamic sensitivities, prior hypotension episodes, or prescriber hesitancy, which would introduce selection bias toward worse baseline prognosis in this treatment group. The absence of SGLT2 inhibitor use data in our dataset further complicates interpretation, as differentials in this emerging GDMT pillar may independently influence readmission risk. Taken together, these considerations signify that MRA monotherapy alone, appears insufficient in real-world clinical settings to meaningfully reduce short-term rehospitalization which should prompt clinical attention to combination GDMT optimization prior to discharge. As with the finding above, this observation should be interpreted as an association rather than evidence of a direct causal shortfall of MRA based therapy, given that treatment was not randomized and patients receiving MRA alone likely differed systematically from those receiving combination therapy. Contemporary evidence, including the FINEARTS-HF trial of finerenone and the pooled

analysis of PARAGLIDE-HF and PARAGON-HF in HFpEF, continues to refine our understanding of MRA and ARNI based therapy across the ejection fraction spectrum, and we encourage readers to consider our findings alongside this evolving body of evidence.

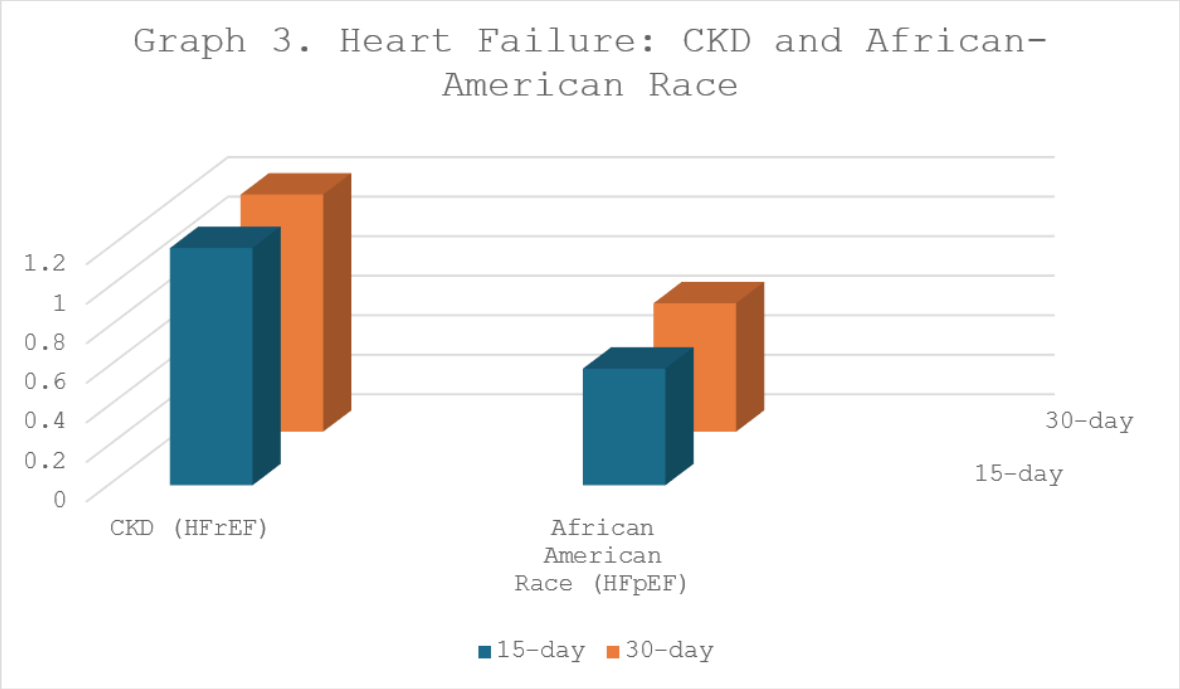
African American Race and HFpEF: A Novel and Hypothesis-Generating Signal

Among the most intriguing and provocative findings of this study is the observation that African American race was independently associated with significantly reduced 15-day (OR 0.59; 95% CI 0.42–0.83; p=0.002) and 30-day (OR 0.65; 95% CI 0.49–0.85; p=0.002) readmission rates among patients with HFpEF. This stands in contrast to findings from several prior investigations, including subgroup analyses from the TOPCAT trial, which enrolled 3,445 patients with symptomatic HFpEF (LVEF ≥45%) and, while its primary composite endpoint of cardiovascular death, aborted cardiac arrest, and HF hospitalization was not significantly reduced by spironolactone overall (HR 0.89; 95% CI 0.77–1.04; p=0.14), demonstrated that African American patients enrolled from the Americas carried a higher baseline burden of adverse events [7]. Similarly, analyses from the I-PRESERVE trial and CHARM-Preserved studies have historically documented higher morbidity and greater cardiovascular risk among Black patients with HFpEF, attributed in part to a higher prevalence of hypertension, obesity, and diastolic dysfunction in this population [16].

The divergence between our findings and these prior observations is striking and warrants careful, multidimensional consideration rather than a simplistic biological or pharmacogenomic explanation. Before considering biological explanations, we believe the most parsimonious explanation deserves emphasis. Because readmissions and deaths outside the HCA network were not captured, differential use of emergency or outside network care among Black patients could lead to undercounting of true readmission events in this subgroup, and we consider this ascertainment bias a leading candidate explanation for the signal observed. Beyond this, several additional hypotheses could also help explain these findings. First, it is plausible that evolving improvements in healthcare accessibility and insurance coverage for lower-income and minority populations: accelerated in part by the Affordable Care Act, have disproportionately benefited African American patients in HCA healthcare-affiliated urban and suburban facilities, reducing historically documented access-related disparities in early post-discharge follow-up [17]. Second, differences in cohort-level characteristics between our study and prior RCT; including the younger age range of our population (30–60 years), de novo HF diagnosis, and exclusion of patients on prior GDMT, All of which may have selected for an African American patient subgroup with a relatively preserved functional reserve and a more treatment-responsive profile. Third, evolving genetic and molecular evidence suggests complex, incompletely characterized biological heterogeneity within racial classifications as they relate to myocardial fibrosis, aldosterone sensitivity, and natriuretic peptide metabolism: physiological mechanisms with direct relevance to MRA and ARNI efficacy [18]. We acknowledge that racial categories are imperfect proxies for both genetic ancestry and socioeconomic experience, and that further granular investigation incorporating social determinants of health, genomic data, and detailed comorbidity profiling will be necessary before any mechanistic inference can be drawn from this signal. Clinicians should remain vigilant about individual comorbidity burden across all patient populations, irrespective of racial background, and should not extrapolate population-level observations to individual patient decision-making (Table 3 and Graph 3).

Heart Failure	Variable	Readmission	ODDS Ratio	p-value	Confidence Interval [L.L, U.L]
HFrEF	CKD **	15-day	1.2	0.04	[1.007, 1.593]
		30-day	1.2	0.01	[1.05, 1.531]
HFpEF	African American Race ++	15-day	0.59	0.002	[0.42, 0.83]
		30-day	0.65	0.002	[0.49, 0.85]
**CKD worsens odds of 15- and 30-day readmissions in HFrEF (Heart Failure with reduced Ejection Fraction) significantly. ++African-American Race betters the odds of 15- and 30-day readmissions in HFpEF (Heart Failure with preserved Ejection Fraction) significantly.					

Table 3: Heart Failure relationship with CKD and African American Race.



Graph 3: Heart Failure relationship with CKD and African-American Race.

HFmrEF: A Continuing Therapeutic Enigma

In keeping with the broader body of literature, our analysis of the HFmrEF cohort (n=4,106) yielded no statistically significant differences across the three treatment comparisons at any of the three readmission time points. This finding is not unexpected. HFmrEF remains the least well-characterized of the three HF phenotypes, having only been formally recognized as a distinct entity by the 2016 ESC guidelines and later affirmed by the 2022 AHA/ACC/HFSA framework [2]. The pathophysiology of HFmrEF is heterogeneous, encompassing patients with gradually improving HFrEF (recovering from prior systolic dysfunction), those with slowly progressive HFpEF, and those representing a genuinely distinct intermediate phenotype [19]. This biological diversity likely dilutes the ability of any single observational study, particularly one relying on administrative data to detect treatment-outcome signals. Prior post-hoc analyses of PARADIGM-HF and CHARM-Alternative have suggested some neurohormonal benefit in the HFmrEF range, and real-world registry data from the Swedish HF Registry have shown that RASI/ARNI and beta-blocker use is associated with improved outcomes in HFmrEF [20]. However, no dedicated prospective RCT has yet been completed in this phenotype with adequate statistical power. Our study, consistent with the current state of evidence, is unable to provide definitive guidance on optimal pharmacologic strategy for HFmrEF and reinforces the call from multiple international societies for phenotype-specific, adequately powered clinical trials in this population [3].

Cardio renal Syndrome and the Importance of CKD in HFrEF Outcomes

The association of CKD (any stage) with significantly elevated 15-day (OR 1.20; 95% CI 1.007–1.593; p=0.04) and 30-day (OR 1.20; 95% CI 1.05–1.531; p=0.01) readmission odds among HFrEF patients in our cohort provides compelling real-world evidence that cardio renal syndrome exerts a measurable and clinically meaningful influence on early post-discharge outcomes. Because this association has been well established in prior literature, we view our finding as confirmatory rather than novel [21]. We also note that the modest odds ratios observed, approximately 1.2, together with our use of a broad any stage CKD definition without stratification by eGFR category, suggest that our results likely understate the more pronounced risk known to occur in advanced CKD stages. The interplay between cardiac and renal dysfunction is bidirectional and self-amplifying: reduced cardiac output impairs renal perfusion and promotes neurohormonal activation, while declining renal function limits the safe titration of GDMT agents: particularly MRAs and ARNI, by elevating risks of hyperkalemia and worsening azotemia [10].This creates a clinical

scenario in which the patients most in need of comprehensive GDMT are paradoxically those least able to tolerate it at full dose, an observation with direct implications for discharge planning and post-acute care protocols.

From a therapeutic standpoint, SGLT2 inhibitors represent perhaps the most significant pharmacologic development in cardiorenal management over the past decade, having demonstrated benefits on composite cardiovascular and renal outcomes across multiple landmark trials including DAPA-HF, EMPEROR-Reduced, DAPA-CKD, and CREDENCE [10]. Current evidence demonstrates that SGLT2 inhibitors reduce the risk of primary cardiovascular outcomes by approximately 26% in patients with stage 3/4 CKD, across subgroups with and without type 2 diabetes [11]. The 2024 KDIGO Clinical Practice Guideline for CKD, issued following analysis of evidence through July 2023: carries a Level 1A recommendation for SGLT2 inhibitor initiation in adults with CKD and an eGFR ≥20 mL/min/1.73 m² irrespective of diabetes status, and specifically in those with comorbid heart failure [22]. Regrettably, our dataset did not include data on SGLT2 inhibitor use; either pre-admission or at discharge, which constitutes one of the most significant analytical limitations of this study. We are therefore unable to determine whether differential rates of SGLT2 inhibitor prescription contributed to or moderated the observed cardiorenal readmission signal. We stand firmly aligned with current KDIGO 2024 recommendations and speculate, consistent with the available mechanistic and clinical trial evidence: that initiation of an SGLT2 inhibitor prior to or at the time of discharge in CKD-HFrEF patients would be expected to attenuate early readmission risk [22]. Dedicated prospective investigation of this hypothesis in real-world HCA-derived populations, with granular SGLT2 inhibitor capture, would substantially advance the cardiorenal knowledge base.

Model Discrimination and Analytical Performance

The C-statistics (concordance indices) across EF subgroups and time points in this study ranged from approximately 0.50 to 0.60. While modest, this discriminatory performance is broadly expected and must be interpreted within the inherent limitations of an administrative, encounter-level dataset. A C-statistic in this range indicates that the model performs modestly better than chance in predicting readmission, a finding that likely reflects the fundamental constraints of working with aggregate, de-identified data that lack granular clinical detail such as NYHA functional class at discharge, specific medication doses, natriuretic peptide levels, hemodynamic parameters, or documented outpatient follow-up. The moderate concordance is not, we emphasize, a function of sample size: our cohort of 23,649 patients is more than adequate to detect meaningful associations; but rather reflects the clinical complexity and multidimensionality of post-discharge readmission risk, which is unlikely to be fully captured by any EF-stratified pharmacologic classification alone. We present this transparency regarding model performance as a scientific obligation and as an invitation for future investigators to apply richer clinical variables and machine learning approaches to improve risk discrimination in this domain.

Broader Clinical Implications, Limitations, and Future Directions

This study carries no ambition to revise or supersede the established evidence base from landmark RCTs or the 2022 AHA/ACC/HFSA heart failure guidelines, a framework built on decades of rigorous, methodologically sophisticated investigation. Rather, it aspires to contribute a transparent, honest, and population-level real-world perspective that complements, rather than competes with, the controlled trial evidence. The distinction between these two knowledge domains is not merely semantic; it is clinically fundamental.

In an RCT such as PARADIGM-HF or RALES, medication adherence is monitored, dosing is protocol-driven and closely supervised, patients are selected for physiological stability and the absence of complex comorbidities, and follow-up is systematically enforced [3]. The real world, by contrast, is governed by medication literacy, insurance-driven access barriers, dietary habits, follow-up adherence, social support structures, and the clinical judgment of individual prescribers navigating complexity not easily categorized by protocol criteria. The patients in our cohort: many with multimorbidity, from geographically and socioeconomically diverse backgrounds, treated in emergency settings: represent a population whose characteristics may differ substantially from those enrolled in canonical HF trials. These differences do not diminish the validity of trial evidence; they contextualize it.

We sincerely encourage clinicians to resist the temptation to apply population-level evidence without adequate individualization. The decision to initiate ARNI, MRA, or combination therapy in a newly diagnosed HF patient should account for real-world factors including baseline blood pressure and heart rate, baseline renal function and potassium levels, concurrent nephrotoxic exposures, access to outpatient follow-up, health literacy, and patient-expressed preferences. The 2022 AHA/ACC/HFSA guidelines themselves emphasize shared decision-making and the importance of maximally tolerated: rather than maximally prescribed GDMT [3]. This nuance is easily lost in summary tables and quality metrics, but is precisely where clinical judgment adds irreplaceable value.

Future investigations building upon the foundation of this study should seek to address several of the limitations we have identified. These include: (1) incorporation of SGLT2 inhibitor use as a critical covariate or stratification variable; (2) cause-

specific readmission analysis rather than all-cause outcomes; (3) extended follow-up beyond 30 days to capture medium-term outcomes; (4) granular comorbidity co-occurrence analysis to better characterize cardiorenal and metabolic syndromic burden; (5) sex-stratified analyses with adequate representation of female patients; and (6) pharmacogenomic sub-stratification, particularly in African American patients with HFpEF, to better understand the biological underpinnings of the observed protective associations. The HCA Healthcare dataset, with its ongoing national reach and longitudinal infrastructure, is uniquely positioned to support such investigations.

We close by reaffirming the spirit with which this work was undertaken: not to challenge the science that has defined modern heart failure care, but to hold up a mirror to the real-world application of that science, with humility about what it reveals, and hope for what it inspires. Our patients deserve not only the evidence our trials have produced, but the clinical wisdom to translate that evidence thoughtfully and equitably across the full spectrum of human experience. We include this closing reflection deliberately, alongside the analytic findings above, to convey the intent behind this work, though we recognize it is offered as context rather than as additional data.

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