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ORIGINAL RESEARCH

OUTCOMES AND QUALITY

Discriminative Ability of Left Ventricular Strain in Mildly Reduced Ejection Fraction Heart Failure

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ABSTRACT

BACKGROUND Left ventricular (LV) systolic strain is presumably a more sensitive myocardial indicator than LV ejection fraction (LVEF). Data regarding the use of LV strain in clinical risk stratification and in identifying angiotensin receptor-neprilysin inhibitor (ARNi) responders remain scarce in heart failure with mildly reduced ejection fraction (HFmrEF).

OBJECTIVES The authors aimed to examine whether assessing LV strain may provide prognostic insight beyond LVEF and help discriminate the therapeutic efficacy of ARNi in HFmrEF patients.

METHODS LVEF and LV strain were quantified among 1,075 first-time hospitalized HFmrEF patients (mean age: 68.1 ± 15.1 years, 40% female). The MAGGIC (Meta-analysis Global Group in Chronic Heart Failure) risk score and its components were calculated. A Cox proportional hazard model was constructed for time-to-event analysis. Restrictive cubic spline curves were used to model the therapeutic effects of ARNi against renin-angiotensin system inhibitor according to baseline LVEF or LV strain.

RESULTS LV strain showed a statistically significant inverse association with MAGGIC cardiac risk (coefficient: −0.14, $P < 0.001$). LV strain was independently associated with clinical outcomes after accounting for LVEF. MAGGIC-LV strain strata outperformed MAGGIC-LVEF strata in overall survival (Harrell's C-index: 0.71 and 0.56, P for difference <0.001; category-free net reclassification index: 0.44, $P < 0.001$). Lower LV strain but not LVEF consistently showed the beneficial therapeutic effects of ARNi against renin-angiotensin system inhibitor by Cox models and restrictive cubic spline (all $P_{interaction}$ <0.05).

CONCLUSIONS Among HFmrEF patients, LV strain may serve as an attractive systolic marker and provide a better prognostic and therapeutic discriminative measure for ARNi treatment than conventional LVEF. (JACC Adv 2023;2:100654)

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ABBREVIATIONS AND ACRONYMS

ARNi = angiotensin receptor neprilysin inhibitor

CV = cardiovascular

HFmrEF = heart failure with mildly reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HHF = heart failure hospitalization

LV = left ventricular

LVEF = left ventricular ejection fraction

MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure

RASi = renin-angiotensin system inhibitor

Heart failure (HF) remains a global public health threat with a high burden of comorbidity and mortality.[1] As a complex clinical syndrome, HF comprises a wide range of the clinical spectrum and several overlapping phenotypes classified using the state of the global left ventricular ejection fraction (LVEF), mainly as reduced (heart failure with reduced ejection fraction [HFrEF], LVEF ≤40%), mildly reduced (heart failure with mildly reduced ejection fraction [HFmrEF], LVEF: >40%, <50%), or preserved LVEF (heart failure with preserved ejection fraction [HFpEF], LVEF ≥50%) HF.[2,3] Despite continuous advances in contemporary HF care and pharmacological approaches, further attempts to improve overall survival in HFmrEF and HFpEF are still showing limited progress.[4,5] Further, there remains a gap in prospective HF trials specifically assessing the therapeutic efficacy of sacubitril/valsartan on patients with LVEF ranging from 35% to 45%, with a narrow LVEF window of 45% to 50% tested only in the PARAGON-HF study.

Despite the success of HFrEF by angiotensin receptor-neprilysin inhibitor (ARNi) to renin-angiotensin system inhibitor (*RASi*) in the PARADIGM-HF HFrEF trial,[6] ARNi only showed benefits over RASi in patients manifesting with a relatively lower LVEF (<57%) in the PARAGON-HF (HFpEF) trial.[7] These findings raised a dispute about the methodological myths in defining the lower boundary of normal LVEF and potential HF therapeutic utilization of ARNi in relation to systolic function.[7,8] Albeit as a convenient parameter in daily practice, accumulating data has suggested that assessing cardiac performance by LVEF remains a poor indicator in delineating true left ventricular (LV) systolic function. As an endocardial measure, LVEF is subject to measurement bias and variations leading to suboptimal accuracy and can mischaracterize true LV systolic function.[9] By contrast, global LV strain has emerged as a reliable and more sensitive myocardial marker capable of identifying subclinical systolic functional declines even when LVEF is preserved.[10-12] Previous studies have also demonstrated the clinical feasibility and superiority of LV strain across a broad spectrum of HF phenotypes beyond LVEF,[11-13] although its clinical prognostic utilization and therapeutic application in HFmrEF remained largely unexplored.

To better address whether adopting LV strain as an alternative systolic index may provide added clinical insights beyond those obtained by LVEF among HFmrEF, we conducted a retrospective analysis using a large-scale real-world dataset. We also aimed to investigate whether LV strain conveys discriminatory capability regarding the therapeutic benefit from sacubitril/valsartan among HF patients with mildly reduced LVEF.

METHODS

STUDY COHORT. Between January 1, 2014, and December 31, 2021, the Echocardiography Core Laboratory pooled from 2-center dataset (both Taipei and Tamsui branches, MacKay Memorial Hospital) was queried to identify first-time hospitalized HF patients presenting with LVEF ranging from 40% to 50% by 2-dimensional (2D) Biplane Simpson quantification. A total of 1,667 patients with adjudicated HF hospitalization met our LVEF criteria as HFmrEF for inclusion according to updated 2022 ACC/AHA HF guideline and DELIVER trial definition.[14,15] HF with improved LVEF (HFimpEF) in current study is defined as HF with previously reduced LVEF (≤40%) and increased to >40%.[15] Settings and detailed information of our HF Core Laboratory dataset have been previously published.[16,17] All demographic, clinical, and laboratory information were extracted from electronic medical records. To examine whether lower LV strain may serve as a marker in determining the treatment efficacy of ARNi against RASi as our study objective, we selected the 1,174 patients (out of 1,667) with either RASi or ARNi treatment as our final study population (493 patients with no use of either RASi or ARNi were excluded). Of those, 1,075 (91.6% available, 280 ARNi vs 795 RASi) had sufficient image quality for both quantitative LVEF and LV strain analysis (as time 0). We categorized the study participants into 2 groups as RASi users (the control group) and ARNi users (ARNi treatment group) (**Table 1**). Among the ARNi users, 69 (24.6%) were treated for HFrEF indication (prior LVEF by 2D ≤40% with current LVEF >40%), and 211 (75.4%) were

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prescribed for misclassified HFrEF indication by linear LVEF determination with LVEF >40% by 2D. All clinical events were followed up until July 1, 2022, and thereafter, the data were frozen and analyzed 1 month later. The detailed study schematic diagram and exclusion criteria are displayed in **Figure 1**. The present study was approved by the local institutional ethics committee (IRB: 18MMHIS133, 21MMHIS052e by MacKay Memorial Hospital, Taipei) and conforms to the ethical guidelines as laid down in the Declaration of Helsinki.

ECHOCARDIOGRAPHY AND LV STRAIN. The LV volumes and subsequent LVEF were quantified by the Biplane Simpson method. Comprehensive cardiac structural and diastolic functional assessment was obtained using standardized protocols according to guideline recommendations,[18,19] including mitral inflow deceleration time, isovolumic relaxation time, LV filling estimate E/e′ (e′ from lateral mitral annulus), and tricuspid regurgitant velocity. Longitudinal LV strain information for each study participant was extracted using a dedicated commercial platform (AutoSTRAIN, TomTec Imaging Systems) offline from digitalized Digital Imaging and Communications in Medicine (DICOM) images with automatic endocardial contour detection with minimal manual tracing. In the present study, representative global LV deformational strain was derived from the average of 3 LV apical views (2-, 3-, and 4-chamber) from 3 continuous heart cycles. For statistical ease, we presented global LV strain by using absolute values $|x|$. Hence, greater numerical value of LV strain indicated better LV myocardial systolic function. Detailed information about the criteria used for selecting sufficient image quality and LV strain reproducibility data from our laboratory were described in our previous publication.[20]

MAGGIC SCORE. The Meta-Analysis Global Group in Chronic heart failure (MAGGIC) score was assessed, a well-validated framework for discerning the integrated clinical information and disease burden (including demographic MAGGIC score, cardiac [as cardiovascular (CV) MAGGIC score], and extra-cardiac risk factors [as non-CV MAGGIC]).[21]

OUTCOMES. In the present study, we prespecified our primary outcome measures as all-cause death and composite CV death and HF hospitalization

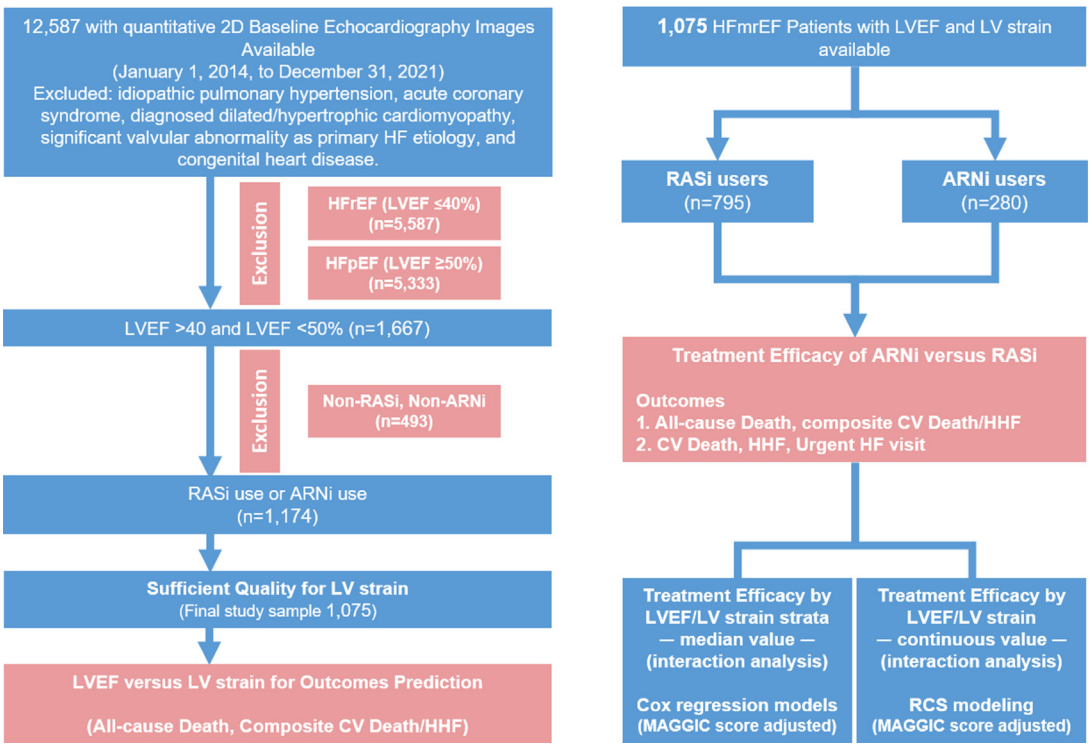
TABLE 1 Study Population Characteristics Stratified by ARNi Treatment or RASi Control

	All Participants (N = 1,075)	RASi Control (n = 795)	ARNi Treatment (n = 280)	*P* Value
Demographics				
Age (y)	68.1 ± 15.1	68.3 ± 15.1	67.6 ± 14.9	0.52
Male	61.0	60.5	62.5	0.56
Body mass index (kg/m^2)	25.1 ± 5.1	25.1 ± 5.1	25.2 ± 5.2	0.77
Systolic blood pressure (mm Hg)	136.5 ± 25.8	135.0 ± 26.4	140.9 ± 23.6	0.001
Heart rate (beats/min)	77.3 ± 27.6	79.8 ± 28.3	70.3 ± 24.2	<0.001
NYHA functional class				0.016
I	5.0	6.2	1.8	
II	66.9	66.0	69.3	
>II (III/IV)	28.1	27.8	28.9	
QRS duration (ms)	106.8 ± 26.5	107.0 ± 26.8	106.2 ± 25.7	0.46
Laboratory				
NT-proBNP (pg/ml) (N = 920)	1,068 [186-3,396]	1,085 [200-3,520]	929.5 [175-3,320]	0.26
Hemoglobin (g/dL)	12.0 ± 2.42	11.9 ± 2.45	12.0 ± 2.34	0.59
eGFR (mL/min/1.73 m^2)	66.5 ± 32.2	66.2 ± 32.7	67.7 ± 30.7	0.48
Comorbidities				
Diabetes mellitus	44.1	46.8	36.4	0.003
Hypertension	56.9	57.0	56.8	0.95
Myocardial infarction	37.7	38.7	34.6	0.22
Coronary artery disease	46.3	47.0	44.3	0.43
Stroke	14.9	15.1	14.3	0.74
Atrial fibrillation	29.6	30.2	27.9	0.46
HFimpEF	24.1	23.9	24.6	0.80
Medication				
Beta-blocker uses	58.6	55.1	68.6	0.001
MRA uses	66.1	63.4	73.9	0.001
MAGGIC HF score				
Total MAGGIC score	23.16 ± 8.48	23.4 ± 8.63	22.6 ± 8.10	0.16
CV MAGGIC score	6.6 ± 2.7	6.4 ± 2.7	6.9 ± 2.5	0.01
Non-CV MAGGIC score	8.1 ± 4.2	8.3 ± 4.3	7.5 ± 3.9	0.003
Demographic MAGGIC score	8.5 ± 5.5	8.6 ± 5.5	8.3 ± 5.6	0.41
Echocardiography				
Septal thickness (mm)	9.9 ± 1.8	9.8 ± 1.8	10.0 ± 1.9	0.18
Posterior wall thickness (mm)	10.1 ± 1.8	10.2 ± 1.9	10.1 ± 1.7	0.60
LV internal diameter (mm)	52.9 ± 7.0	52.9 ± 7.0	52.8 ± 6.9	0.91
LVEF (%)	44.7 ± 2.3	44.7 ± 2.1	44.9 ± 2.8	0.20
LV mass index (g/m^2)	111.4 ± 36.9	111.9 ± 36.7	110.2 ± 37.4	0.51
Deceleration time (ms)	198.4 ± 72.9	196.5 ± 73.6	204.1 ± 70.8	0.13
Isovolumic relaxation time (ms)	94.7 ± 30.0	94.1 ± 29.4	96.5 ± 31.6	0.24
TR velocity (m/s)	2.7 ± 0.5	2.7 ± 0.5	2.7 ± 0.5	0.78
LV strain (%)	12.3 ± 2.7	12.3 ± 2.6	12.4 ± 3.0	0.43
E/e′	13.8 ± 6.8	14.0 ± 6.9	13.4 ± 6.7	0.26

Values are mean ± SD, %, or median [25th-75th interquartile range].

ARNi = angiotensin receptor-neprilysin inhibitors; E/e′ = mitral peak E velocity to average e′; eGFR = estimated glomerular filtration rate; HFimpEF = heart failure with improved ejection fraction; LVEF = left ventricular ejection fraction; MAGGIC = Meta-Analysis Global Group in Chronic heart failure risk score; MRA = mineralocorticoid receptor antagonist; RASi = renin-angiotensin system inhibitors; TR = tricuspid regurgitation.

FIGURE 1 Schematic Flowchart Shows the Eligible and Exclusion Criteria and Study Assignment in the Present Study

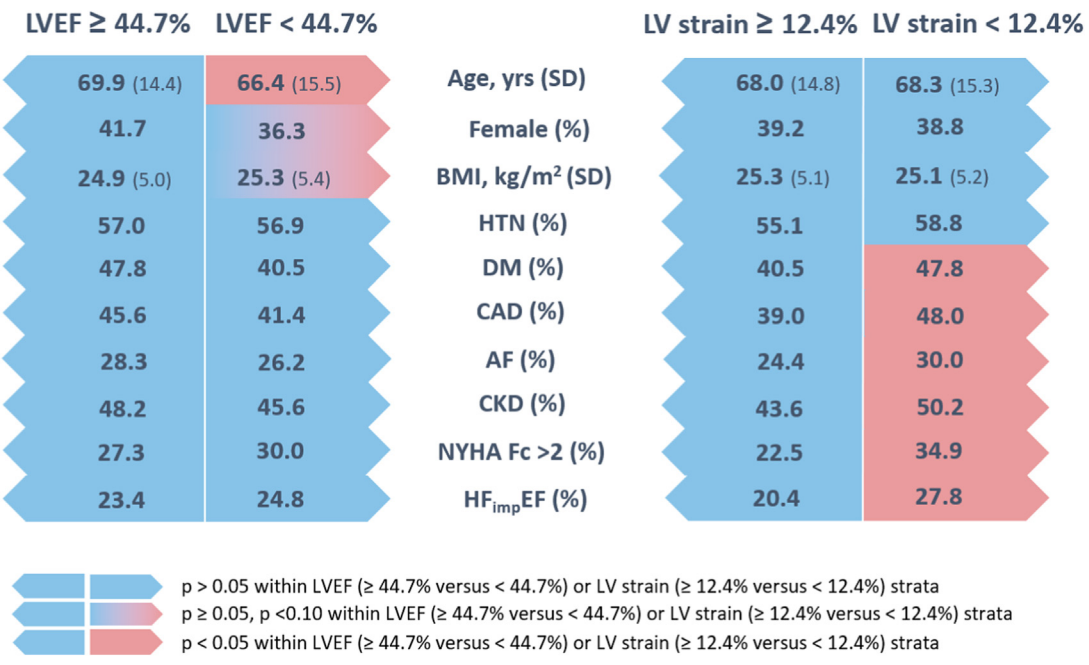


(HHF), with secondary endpoints being HHF, CV death, and urgent HF visit. We further examined the prognostic utilization of LV strain among our HFmrEF population.

STATISTICAL METHODS. Symmetrically distributed continuous data are expressed as mean ± SD. Categorical variables were compared using either Fisher's exact test or the chi-square test with a Yates correction, as appropriate. Independent *t*-test (for any 2 groups) was used for the comparative analysis of continuous variables. Pearson correlation was used to test the linear correlations among LVEF, LV strain, and MAGGIC score. Univariable and multivariable (by MAGGIC score) Cox proportional hazard regression models were used to examine the event-free survival on outcomes measures, with the Fine and Gray subdistribution hazards model accounting for the competing risk of all-cause death in models of clinical events. Schoenfeld residual test showed no violation of proportional hazards assumption. The Kaplan-Meier method was used to estimate the survival function for lifetime data. The log-rank test was used for time-to-event comparisons among all groups. All patients underwent follow-up until death or last contact.

To visualize and delineate the associations of primary outcome measures with LVEF and LV strain, we further tested the linearity relationship between various baseline LV systolic parametric indices (including LVEF and LV strain as continuous variables) and endpoints using restricted cubic spline curves (RCS) with spline knots selected based on 3 cutoff points besides the lower (fifth) and upper (95th) percentile threshold values. We further applied the RCS to model the relationships between baseline LVEF or LV strain (modeled as a natural flexible spline) and ARNi treatment effect (against RASi use as an interaction term) to explore whether there were LVEF- or LV strain-dependent effects on primary endpoints (all-cause death and composite CV death/HHF) fitted by the Cox proportional hazard model. We used 4 knots at the 5th, 35th, 65th, and 95th percentiles. The HR of ARNi users vs non-ARNi users and its 95% CI across continuous LVEF and LV strain measures were obtained.

FIGURE 2 Association of Clinical Baseline Characteristics and Comorbidities With LVEF and LV Strain Strata (Both by Median Values)



AF = atrial fibrillation; BMI = body mass index; CAD = coronary artery disease; CKD = chronic kidney disease (eGFR <60 mL/min/1.73 m^2); DM = diabetes mellitus; HFimpEF = heart failure with improved ejection fraction; HTN = hypertension; LVEF = left ventricular ejection fraction; NYHA Fc = New York Heart Association functional class.

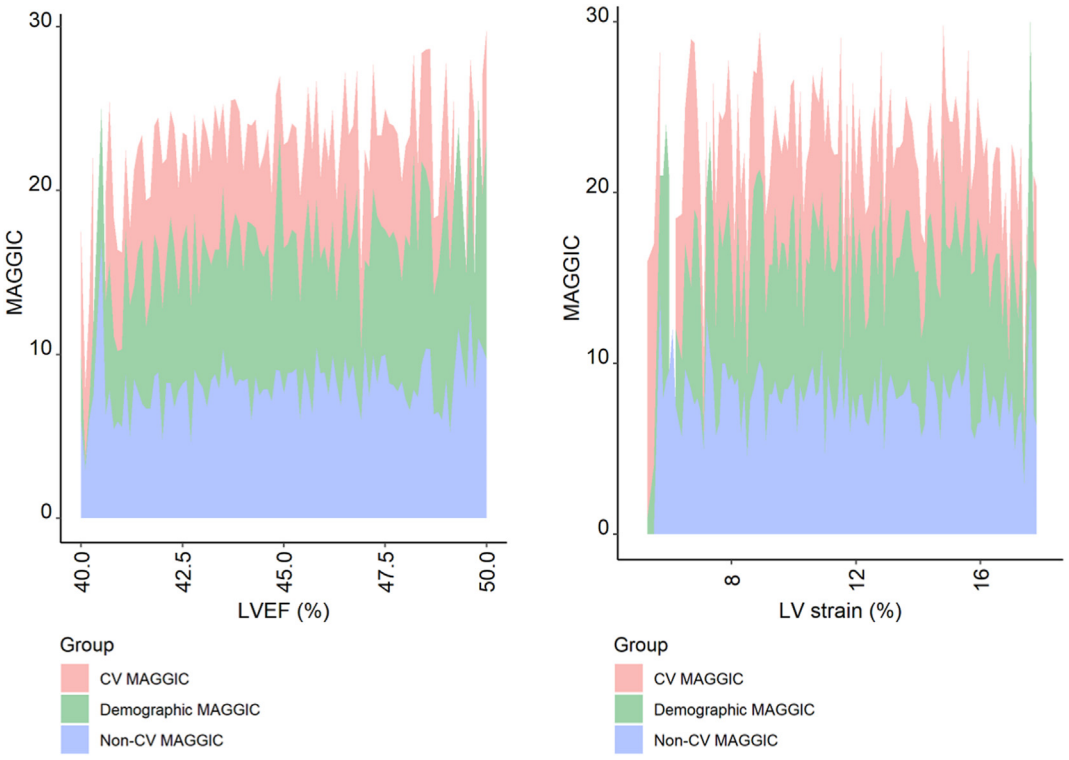
All analyses were performed using STATA 14.0 software (Stata Corp) and R software (version 4.0.2, R Foundation for Statistical Computing) with the 'rms' package for restricted cubic spline modeling. All *P* values were 2-tailed, with $P < 0.05$ considered statistically significant.

RESULTS

PATIENTS DEMOGRAPHICS. Table 1 shows the baseline characteristics and echocardiographic features among the 1,075 eligible HFmrEF study participants (mean age: 68.1 ± 15.1 years, 40% female). The participants in the RASi group had lower baseline blood pressure, higher heart rate, higher prevalence of diabetes, and lower use of beta-blocker compared to the ARNi group (Table 1). LV strain showed a modest yet significant relationship with LVEF (r = 0.27, $P < 0.001$). The mean LVEF and LV strain in present study were 44.7% ± 2.3% and 12.3% ± 2.7%, respectively, and they did not significantly differ between the ARNi and RASi groups ($P = 0.20$ and $P = 0.43$ for LVEF and LV strain, respectively). Disparity in the baseline characters and comorbidities with LVEF (≥44.7% vs <44.7%) and LV strain (≥12.4% vs <12.4%) strata (derived from each median value) are displayed in Figure 2. Worse LV strain generally was accompanied by several unfavorable comorbid conditions, including higher prevalence of diabetes, coronary artery disease, atrial fibrillation, lower estimated glomerular filtration rate, and worse New York Heart Association functional class. By contrast, higher LVEF was associated with more advanced age.

LV STRAIN AND MAGGIC SCORE. Overall, LVEF showed positive correlations with the MAGGIC score, demographic score (Coef. = 0.55 and 0.39, both $P < 0.001$), and its non-CV component (Coef. = 0.18, $P = 0.001$), with nonsignificant association found with MAGGIC cardiac risk factors (as CV MAGGIC score) (Coef. = −0.02, $P = 0.49$) (Figure 3); by contrast, LV strain marginally correlated with the MAGGIC score (Coef. = −0.22, $P = 0.022$) and showed

FIGURE 3 Distribution Graphs of the Individual MAGGIC Risk Factors (as Y-Axis) Across the Continuous LVEF and LV Strain Values (Both as X-Axis)



CV MAGGIC = cardiac MAGGIC risk factors; LVEF = left ventricular ejection fraction; Non-CV MAGGIC = extra-cardiac MAGGIC risk factors.

significant inverse correlation with the CV MAGGIC score (Coef. = −0.14, $P < 0.001$) (Table 2).

LV STRAIN IN HFimpEF. Prevalent HFimpEF was significantly higher in worse LV strain strata and was comparable in LVEF strata (Supplemental Figure 1A). LVEF showed a nonsignificant difference (44.6% vs 44.8%, $P = 0.22$) between those recovered from HFrEF (as prevalent as HFimpEF) and those without known HFrEF (n = 259 and n = 816, respectively). Instead, significantly lower LV strain was observed in those recovered from HFrEF (as prevalent as HFimpEF) compared to non-HFimpEF subgroup (11.80% vs 12.47%, $P < 0.001$). Among those classified as HFimpEF, shorter LV recovery interval from HFrEF to HFmrEF was associated with significant and graded reduction of LV strain (12.5% ± 2.3%, 11.9% ± 2.6%, and 10.8% ± 2.6% for ≤3 months, 3-12 months, and ≥1 year, respectively; P for trend <0.001) albeit no substantial differences in LVEF were found (44.7% ± 2.1%, 44.7% ± 1.8%, and 44.2% ± 2.2%, respectively; P for trend = 0.11) (Supplemental Figure 1B), indicating the potential of LV contractile recovery over time, assessed by LV strain.

TABLE 2 Associations of Individual MAGGIC Components With LVEF and LV Strain Reduction

	LVEF (%)		LV Strain (%)	
	Coef. (95% CI)	*P* Value	Coef. (95% CI)	*P* Value
Total MAGGIC score	0.55 (0.33 to 0.76)	<0.001	−0.22 (−0.40 to −0.03)	0.022
CV MAGGIC score	−0.02 (−0.09 to 0.05)	0.49	−0.14 (−0.20 to −0.08)	<0.001
Non-CV MAGGIC score	0.18 (0.07 to 0.28)	0.001	−0.05 (−0.14 to 0.04)	0.27
Demographic MAGGIC score	0.39 (0.25 to 0.54)	<0.001	−0.03 (−0.15 to 0.10)	0.68

Coef. = coefficients; CV = cardiac; MAGGIC = Meta-Analysis Global Group in Chronic heart failure risk score.

IMPROVED PROGNOSTIC STRATIFICATION WITH LV STRAIN COMPARED TO LVEF. While LVEF alone failed to identify the risk of all-cause death and composite CV death/HHF (Harrell's C-index: 0.50 and 0.54, P value for crude Cox models: 0.16 and 0.15, respectively) (using the Fine and Gray model) during a median of 1.80 years (IQR: 0.54-3.99 years)

follow-up, by contrast, worse LV strain alone performs well on all clinical events in crude and in fully adjusted models (by MAGGIC score) (Table 3, Figure 4). There was no apparent association between LVEF and risk for adverse events; on the contrary, worse LV strain was significantly associated with the development of diverse clinical outcomes (Supplemental Figure 2). Stratified LV strain (≧12.4% vs <12.4%) combined with the MAGGIC category (as MAGGIC-LV strain strata) provided incremental prognostic values to MAGGIC-LVEF strata in overall survival (Harrell C statistic: 0.56 and 0.72 for all-cause death by MAGGIC-LVEF and MAGGIC-LV strain strata, *P* for difference <0.001; category-free net reclassification index: 0.44, $P < 0.001$).

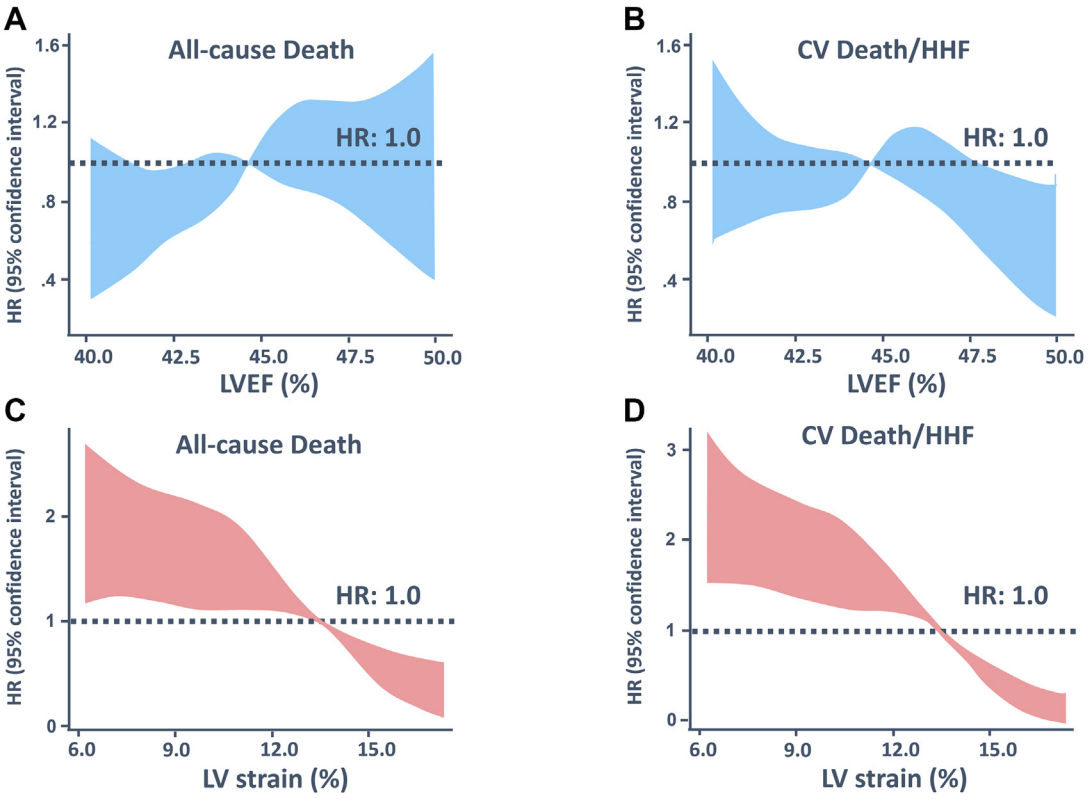
TABLE 3 Prognostic Utilization of LV Strain in Diverse Clinical Endpoints

LV Strain (%) (Predictor)		Crude Effect			Adjusted Model (MAGGIC Score Adjusted)[a]		
Outcome Measures	Harrell's C-Index	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Primary endpoints							
All-cause death	0.67	0.84	0.80-0.88	<0.001	0.85	0.80-0.90	<0.001
CV death + HHF	0.71	0.83	0.80-0.86	<0.001	0.84	0.81-0.87	<0.001
Secondary endpoints							
CV death	0.70	0.81	0.77-0.85	<0.001	0.81	0.77-0.86	<0.001
HHF	0.70	0.82	0.78-0.85	<0.001	0.83	0.80-0.87	<0.001
Urgent HF visit	0.68	0.83	0.79-0.87	<0.001	0.84	0.80-0.89	<0.001

[a]LVEF was added in models.

CV = cardiovascular; HHF = HF hospitalization; LV = left ventricular; MAGGIC = Meta-Analysis Global Group in Chronic heart failure risk score.

FIGURE 4 The Relationships Between LVEF or LV Strain and Outcomes



Restrictive cubic splines (RCS) for modelling relationships between continuous LVEF (A and B) and LV strain (C and D) values (both units: %) on primary endpoints of all-cause death and composite CV death/HHF, respectively. CV = cardiovascular; HHF = HF hospitalization.

TABLE 4 Therapeutic Benefits From ARNi Treatment Versus RASi Use by LVEF and LV Strain Strata

(MAGGIC Score Adjusted Model)		ARNi vs RASi								
		All Participants			LVEF <44.7%			LVEF ≥44.7%			
	LVEF (%) Outcome Measures	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	$P_{interaction}$
LVEF strata	Primary endpoints										
	All-cause death	0.76	0.54-1.08	0.12	0.72	0.40-1.30	0.28	0.81	0.51-1.29	0.37	0.48
	CV deaths + HHF	0.70	0.53-0.94	0.03	0.57	0.38-0.85	0.01	0.79	0.54-1.18	0.23	0.28
	Secondary endpoints										
	CV death	0.70	0.46-1.06	0.086	0.49	0.23-1.05	0.07	0.85	0.49-1.43	0.54	0.10
	HHF	0.63	0.46-0.90	0.01	0.64	0.40-1.01	0.06	0.67	0.40-1.10	0.10	0.95
	Urgent HF visit	0.43	0.28-0.69	0.007	0.43	0.23-0.81	0.01	0.44	0.24-0.83	0.01	0.93
		All Participants			LV Strain <12.4%[a]			LV Strain ≥12.4%[a]			
	LV Strain (%) Outcome Measures	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	$P_{interaction}$
LV strain strata	Primary endpoints										
	All-cause death	0.76	0.54-1.08	0.12	0.54	0.34-0.87	0.012	1.26	0.68-2.48	0.24	0.018
	CV death + HHF	0.70	0.53-0.94	0.03	0.54	0.38-0.79	0.001	1.07	0.67-1.70	0.77	0.018
	Secondary endpoints										
	CV death	0.70	0.46-1.06	0.086	0.47	0.27-0.83	0.008	1.50	0.78-2.88	0.23	0.017
	HHF	0.63	0.46-0.90	0.01	0.46	0.29-0.73	0.001	1.08	0.63-1.83	0.78	0.007
	Urgent HF visit	0.43	0.28-0.69	0.007	0.29	0.16-0.55	<0.001	0.80	0.41-1.57	0.51	0.024

[a]LVEF was added in models. Fine and Gray subdistribution hazards models used accounting for the competing risk of all-cause death.

ARNi = angiotensin receptor-neprilysin inhibitor; CV = cardiovascular; HHF = HF hospitalization; LV = left ventricular; LVEF = left ventricular ejection fraction; $P_{interaction}$ = *P* interaction (ARNi treatment × LVEF or LV strain strata).

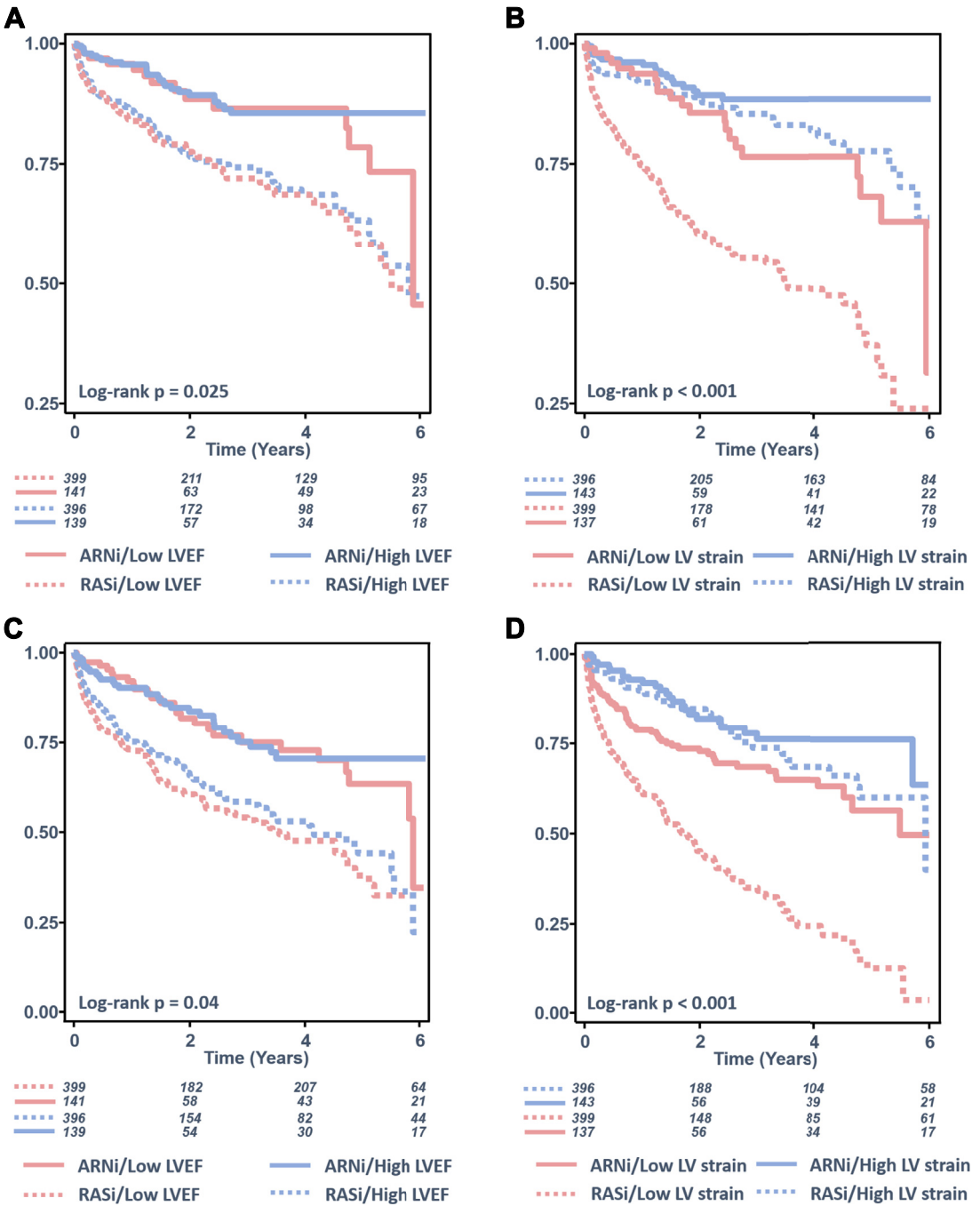
THERAPEUTIC BENEFITS OF ARNi STRATIFIED BY LV STRAIN. In the present cohort, the use of valsartan/sacubitril therapy (n = 280) was associated with slightly lower all-cause deaths and CV death (HR: 0.71, 95% CI: 0.50-1.01; HR: 0.65, 95% CI: 0.43-0.99, $P = 0.06$ and 0.043, respectively) compared to the use of RASi (Supplemental Table 1), which could have been confounded by imbalanced demographics or treatment backgrounds (Table 1). As the MAGGIC score encompassed nearly all unbalanced baseline features between the 2 treatment groups, multivariable adjustment for MAGGIC score showed attenuated benefits of valsartan/sacubitril use on multiple outcomes, especially on survival function (Supplemental Table 1). A nominally significant interaction between baseline LV strain strata (by median value 12.4%) and the effect of ARNi treatment vs RASi on the primary and secondary endpoints was found (Supplemental Table 2) even with adjustment (using the Fine and Gray model) (all adjusted $P_{interaction} < 0.05$) (Table 4), which was not seen for the interaction between LVEF strata (by median value 44.7%) and the effect of ARNi treatment on all outcomes (all P = NS). The Kaplan-Meier survival estimates and log-rank test results according to LVEF/LV strain strata and medication group (ARNi vs RASi) are shown in Figure 5. The continuous LVEF and LV strain treated as flexible RCS demonstrating the LVEF- or LV strain-dependent treatment efficacy of ARNi vs RASi uses are shown in Figure 6.

DISCUSSION

In the present study, we demonstrated that in HF patients within a narrow LVEF range (40%-50%), global LV strain, rather than LVEF, was closely associated with clinical comorbidities, functional status, and cardiac risk burden, and identified those HF individuals who recovered from impaired systolic LV function (from HFrEF to HFmrEF as HFimpEF). LV strain further improved risk stratification of clinical outcomes. The treatment sacubitril/valsartan efficacy appeared to be amplified among those classified into the lower LV strain category, albeit no such relations were found by LVEF strata. Our findings suggest that among HF patients presenting mildly reduced LVEF (40%-50%), compared to LVEF, introducing myocardial strain may inform better clinical characterization with improved risk stratification than LVEF and is also clinically implicated in distinguishing those who may benefit from ARNi treatment.

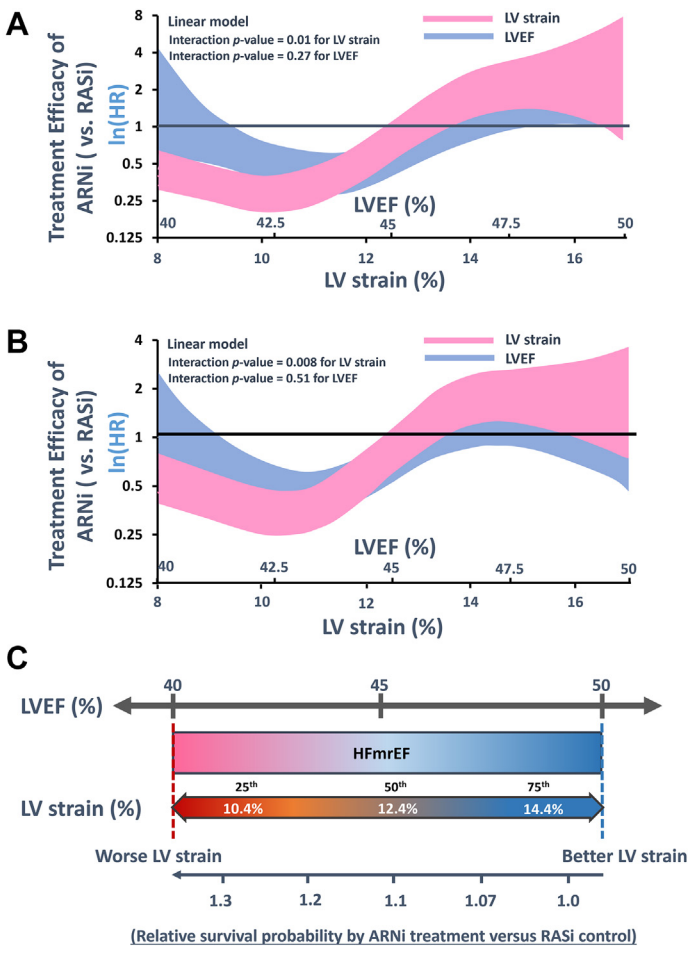
Findings from epidemiological and registry data have demonstrated that HF individuals manifesting higher LVEF (eg, HFpEF) was more commonly associated with multiple clinical comorbidities or etiologies, yet the number of comorbidities diminishes in

FIGURE 5 The Kaplan-Meier Survival Curves Stratified by LVEF/LV Strain and ARNI Use



The Kaplan-Meier survival estimates and log-rank test results according to LVEF and LV strain strata (upper and lower categories by median values) and pharmacological intervention (ARNi vs RASi control) with respect to primary endpoints of all-cause death (A and B) and composite CV death/HHF (C and D), respectively. CV = cardiovascular; HHF = HF hospitalization.

FIGURE 6 Relationships of Treatment Efficacy from ARNi Use (versus RASi control) by Continuous LVEF/LV Strain Values



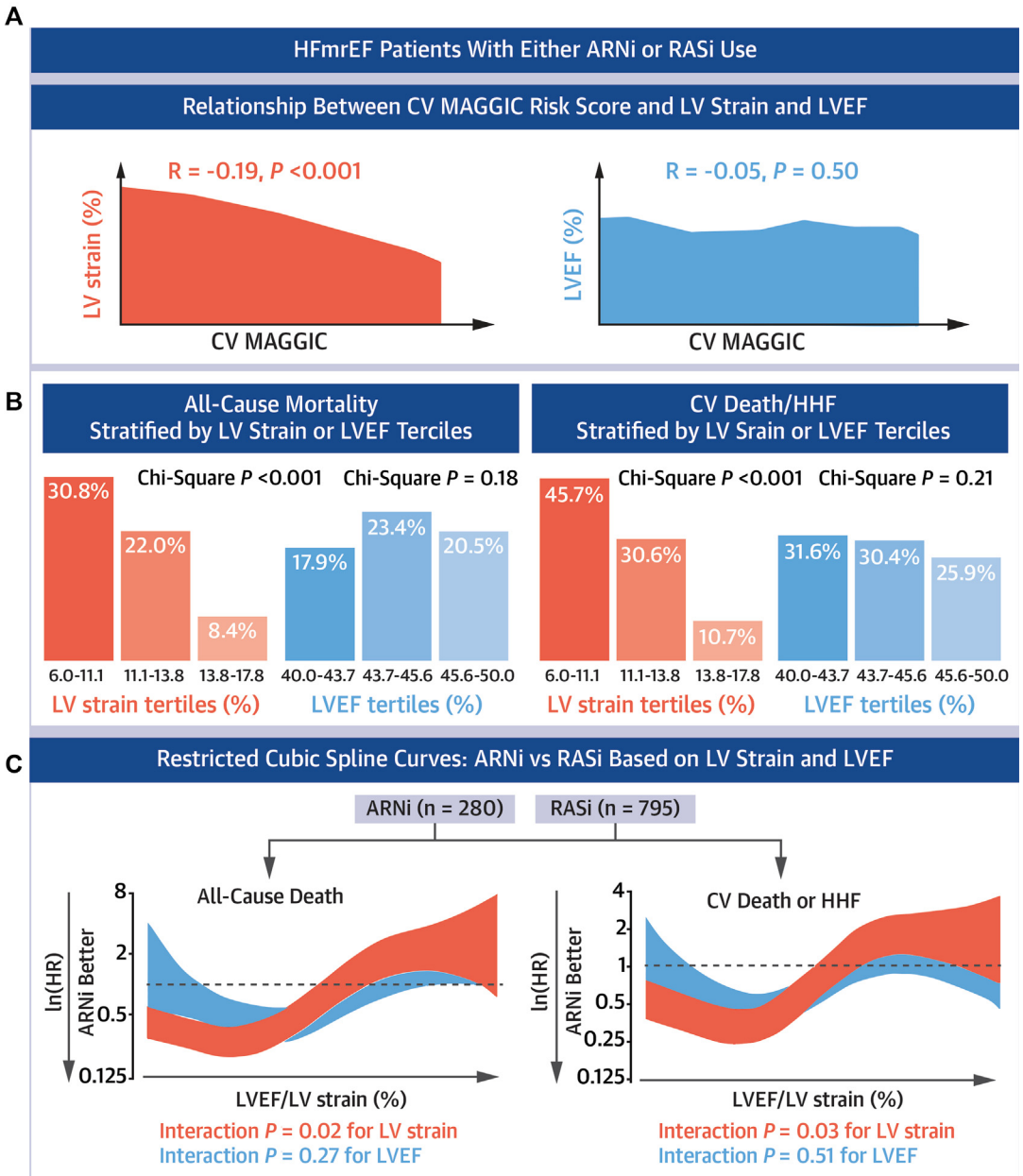
Restrictive cubic splines (RCS) for modelling relationships from ARNi treatment efficacy compared with RASi control across the continuous LVEF and LV strain values on primary endpoints of all-cause death (A) and composite CV death/HHF (B) (MAGGIC score adjusted). (C) Relative survival probability for ARNi compared with RASi control according to LV strain cutoffs (<25th, 25th-50th, 50th-75th, ≥75th percentiles, ≥75th percentile serves as reference) in present study. CV = cardiovascular; HFmrEF = heart failure with mildly reduced LVEF; HFpEF = heart failure with preserved LVEF; HFrEF = heart failure with reduced LVEF; HHF = HF hospitalization; HR = hazard ratio.

the transition between HFpEF and HFrEF, with HFmrEF appears to have intermediate clinical characteristics in between HFrEF and HFpEF.[8,22-24] Interestingly, we observed distinctive presentations of clinical characteristics and comorbid conditions in relation to the LVEF and LV strain strata (**Figure 2**). This finding indicates that clinical categorization of HFmrEF by LVEF and LV strain may not be equal. In general, lower LV strain better reflects the co-existence of key clinical features and comorbid conditions than LVEF. In the present study, impaired LV strain, but not LVEF, was closely related to higher MAGGIC cardiac risks ($r = -0.19$, $P < 0.001$) albeit a marginal correlation was found between LV strain and total MAGGIC score ($r = -0.07$). Numeric increase in MAGGIC scores by LVEF within such range (>40%) were mainly contributed by age and systolic blood pressure. These specific features indicate that global LV strain likely behave biologically different and delineate better clinical CV risks and contractile reserve that cannot be fully captured by chamber-level estimate of LVEF within borderline LVEF 40% to 50% (**Central Illustration A to C**).[25]

To date, LVEF remains the cornerstone for characterizing and guiding therapeutic approaches and has been shown to play a pivotal role as HF prognosticator. However, its clinical use is not without limitations, for example, assessment of LVEF has up to 13% to 21% variations, and the clinical utilization of LVEF may lead to 10% to 15% misclassification.[26,27] In this regard, multiparametric imaging modalities or indicators; for example, cardiac magnetic resonance in identifying the existence of myocardial fibrosis or HF biomarkers from multiple dimensions, have been shown to improve outcome prediction in such patient population.[28,29] Global LV strain as a dimensionless contractility measure has shown superiority in HF outcome prediction across a wide range of LVEF, including those presenting HFpEF.[25,30-33] Our study concept was based on previous research in which LV strain outperformed LVEF in identifying clinical deterioration among optimally treated HF individuals.[34,35] In the present work, LV strain is also capable of characterizing dynamic contractile recovery from reduced LVEF on a temporal basis (Supplemental Figure 1B). Overall, compared to LVEF, LV strain showed prognostic superiority in multiple outcomes in the present work as systolic indicator. Because the addition of LV strain on MAGGIC score further significantly improved the prognostic value compared to that of LVEF, we suggest that LV strain may provide incremental prognostic value beyond LVEF and clinical risks.

In the pooled PARADIGM-HF and PARAGON-HF trials, extrapolation analysis showed limited benefits on primary endpoints from sacubitril/valsartan use within the LVEF category of 42.5% to 52.5%.[36-38] Furthermore, the benefits of sacubitril/valsartan against RASi in PARAGON-HF have been shown to successfully reduce HF hospitalization or urgent HF visits though overall primary composite endpoint including CV mortality was missed, partly due to the limits of the study design.[38,39] In the DELIVER trial testing the efficacy of sodium-glucose cotransporter

CENTRAL ILLUSTRATION **Discriminative Ability of Left Ventricular Strain in Mildly Reduced Ejection Fraction Heart Failure**



Chung F-P, et al. JACC Adv. 2023;2(9):100654.

Relationship between CV MAGGIC risk score and LV strain and LVEF. All-cause mortality stratified by LV strain or LVEF terciles and CV death/HHF stratified by LV strain or LVEF terciles. Restricted cubic spline curves: ARNi vs RASi based on LV strain and LVEF. CV MAGGIC = cardiac MAGGIC risk factors; LVEDV = LV enddiastolic volume; LVEF = left ventricular ejection fraction; LVESV = LV end-systolic volume; RCS = restrictive cubic splines.

2 inhibitor in mildly reduced to preserved ejection fraction (LVEF >40%) HF patients, up to 18.4% of total population who recovered from HFrEF (as HFimpEF) showed a trend toward better therapeutic response (HR: 0.74 vs 0.84 for HFimpEF vs non-HFimpEF).[15] Our data perhaps supplement findings from DELIEVER trial and showed that HF patients recovered from HFrEF may be functionally more vulnerable featuring a more impaired LV strain (as current study), albeit relatively preserved LVEF, who will likely benefit more from pharmacological intervention. Our present study suggests the relative benefits of sacubitril/valsartan against RASi on overall survival, and HF events appeared to be amplified among HFmrEF patients with lower LV strain, inferring additional therapeutic beneficial from dysregulated neurohormonal activation among HFmrEF patients with more impaired myocardial strain (Supplemental Figure 3, **Central Illustration**).

STUDY LIMITATIONS. Our current findings may have been affected by several limitations. ARNi, as a potent agent in HFrEF treatment, was not officially (on label) declared for use in HFmrEF during our retrospective study observation period, and therefore the sample size in the present study is relatively small. Therefore, our findings may need to be validated in a future prospective study. Secondly, concerning the ARNi users in present study were mainly misclassified, most of the key baseline demographics were comparable to those RASi using HFmrEF patients and resembled HFmrEF or HFpEF patients from registry data (eg, relatively older age, lower prevalence [<50%] of coronary artery disease, and higher atrial fibrillation percentage) with nonsignificant differences in echocardiographic parameters including LVEF, suggesting true nature representative of the actual HFmrEF population. Third, as HF is a (dynamic) continuum, history of comorbidities and treatment effects of guideline-recommended medications may influence LVEF before entering the HFmrEF stage. As a complete history of any single patient may not be ascertained unless traced from early life, we aimed to explore whether LV strain may confer better clinical information and therapeutic discrimination from ARNi than LVEF in any patient presenting first-time HF hospitalization with LVEF fall within a gray zone of 40% to 50%.

CONCLUSIONS

In HFmrEF, where global LV pump function stays in a marginal zone with poorly defined clinical significance and cardiac systolic features in the context of LVEF, implementing LV systolic strain likely provides additional insights into clinical characteristics, which also better delineates true myocardial performance than LVEF with improved risk stratification. Our data also suggest the advantageous use of LV strain as an alternative yet superior systolic functional metric than LVEF, which can be further clinically implicated in distinguishing therapeutic ARNi benefits within a borderline impaired LVEF category. Further large-scale and prospectively designed randomized controlled studies may be warranted to validate our current study.

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PERSPECTIVES

COMPETENCY IN CLINICAL KNOWLEDGE: HFmrEF (LVEF 40%-50%), a HF phenotype with intermediate clinical features between HFrEF and HFpEF, remains an underexplored clinical HF phenotype with poorly defined myocardial characterization. According to contemporary HF management guideline, ARNi along with most guideline recommended medications for HFrEF were given Class IIb recommendations for HFmrEF except for sodium-glucose cotransporter-2 inhibitors (as a Class IIa recommendation).

TRANSLATIONAL OUTLOOK: LV strain likely provides better insights on clinical comorbid conditions and outperforms LVEF in risk stratification as potentially new "morphofunctional phenotypes" defined by LV strain measure. Additionally, the clinical implementation of LV strain also supplements the current knowledge gap on sacubitril/valsartan use within a HFmrEF in clinical practice.

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KEY WORDS angiotensin receptor neprilysin inhibitor (ARNi), heart failure with mildly reduced ejection fraction, renin-angiotensin system inhibitors (RASi), LV ejection fraction, LV strain, MAGGIC score

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