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Echocardiographic Features of Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction

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ABSTRACT

BACKGROUND The PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction) trial tested the efficacy of sacubitril-valsartan in patients with heart failure with preserved ejection fraction (HFpEF). Existing data on cardiac structure and function in patients with HFpEF suggest significant heterogeneity.

OBJECTIVES The aim of this study was to characterize cardiac structure and function, quantify their associations with clinical outcomes, and contextualize these findings with other HFpEF studies.

METHODS Echocardiography was performed in 1,097 of 4,822 PARAGON-HF patients within 6 months of enrollment. Associations with incident first heart failure hospitalization or cardiovascular death were assessed using Cox proportional hazards models adjusted for age, sex, region of enrollment, randomized treatment, N-terminal pro-brain natriuretic peptide, and clinical risk factors.

RESULTS Average age was 74 ± 8 years, 53% of patients were women, median N-terminal pro-brain natriuretic peptide level was 918 pg/ml (interquartile range: 485 to 1,578 pg/ml), 94% had hypertension, and 35% had atrial fibrillation. The mean left ventricular (LV) ejection fraction was 58.6 ± 9.8%, prevalence of LV hypertrophy was 21%, prevalence of left atrial enlargement was 83%, prevalence of elevated E/e′ ratio was 53%, and prevalence of pulmonary hypertension was 31%. Heart failure hospitalization or cardiovascular death occurred in 288 patients at 2.8-year median follow-up. In fully adjusted models, higher LV mass index (hazard ratio [HR]: 1.05 per 10 g/m^2; 95% confidence interval [CI]: 1.00 to 1.10; $p = 0.03$), E/e′ ratio (HR: 1.04 per unit; 95% CI: 1.02 to 1.06; $p < 0.001$), pulmonary artery systolic pressure (HR: 1.51 per 10 mm Hg; 95% CI: 1.29 to 1.76; $p < 0.001$), and right ventricular end-diastolic area (HR: 1.04 per cm^2; 95% CI: 1.01 to 1.07; $p = 0.003$) were each associated with this composite, while LV ejection fraction and left atrial size were not ($p > 0.05$ for all). Appreciable differences were observed in cardiac structure compared with other HFpEF clinical trials, despite similar E/e′ ratio, pulmonary artery systolic pressure, and event rates.

CONCLUSIONS Diastolic dysfunction, left atrial enlargement, and pulmonary hypertension were common in PARAGON-HF. LV hypertrophy, elevated left- and right-sided pressures, and right ventricular enlargement were independently predictive of incident heart failure hospitalization or cardiovascular death. Echocardiographic differences among HFpEF trials despite similar clinical event rates highlight the heterogeneity of this syndrome. (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction [PARAGON-HF]; NCT01920711) (J Am Coll Cardiol 2019;74:2858–73) © 2019 by the American College of Cardiology Foundation.

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Heart failure with preserved ejection fraction (HFpEF) accounts for approximately one-half of prevalent heart failure (HF) overall (1,2) and ≤70% of prevalent HF in elderly patients (3) and is increasing in prevalence (4). HFpEF is associated with excess mortality (5,6) and similar morbidity following HF hospitalization to HF with reduced ejection fraction (7,8). HFpEF is characterized by abnormalities of left ventricular (LV) structure, diastolic function, and systolic function despite preserved LV ejection fraction (LVEF) (9–11), but the diversity of the cardiac phenotype in HFpEF is now well recognized (12,13). The PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction) trial was designed to determine the long-term efficacy and safety of sacubitril-valsartan compared with valsartan alone in patients with chronic HF with LVEF ≥45%, New York Heart Association (NYHA) functional class II to IV symptoms, elevated natriuretic peptides, and evidence of structural left heart disease (14,15). Assessment of cardiac structure and function by echocardiography at baseline was pre-specified in a subset of participants for the purpose of characterizing the cardiac phenotype in a substantial portion of the trial participants. In this analysis, we describe cardiac structure and function in this HFpEF sample from within 6 months prior to trial enrollment, relate these measures to clinical outcomes, and contextualize these findings with HFpEF in epidemiological studies and other clinical trials.

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METHODS

PATIENT POPULATION. PARAGON-HF was a multicenter, international, randomized, double-blind, event-driven trial testing the long-term efficacy and safety of sacubitril-valsartan compared with valsartan alone in adults patients with signs and symptoms of HF and LVEF ≥45% as previously described in detail (14). Briefly, PARAGON-HF enrolled 4,822 patients at 752 sites in 43 countries who met the following key inclusion criteria: 1) age ≥50 years; 2) symptoms of HF requiring treatment with diuretic agents and with current NYHA functional class II to IV symptoms; 3) LVEF ≥45% per local reading by echocardiography during the screening epoch or within 6 months prior to the screening visit; 4) left atrial (LA) enlargement (≥1 of the following: LA width ≥3.8 cm, LA length ≥5.0 cm, LA area ≥20 cm^2, LA volume ≥55 ml, or LA volume index ≥29 ml/m^2) or septal thickness or posterior wall thickness ≥1.1 cm by local reading; and 5) ≥1 of the following: a) HF hospitalization within 9 months prior to screening and N-terminal pro-brain natriuretic peptide (NT-proBNP) >200 pg/ml for patients not in atrial fibrillation (AF) or atrial flutter or >600 pg/ml for patients in AF on screening electrocardiography; or b) NT-proBNP >300 pg/ml for patients not in AF or >900 pg/ml for patients in AF on screening electrocardiography. Key exclusion criteria

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
ASE = American Society of Echocardiography
CI = confidence interval
CV = cardiovascular
FAC = fractional area change
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
LA = left atrial
LV = left ventricular
LVEF = left ventricular ejection fraction
LVH = left ventricular hypertrophy
LVMi = left ventricular mass index
NT-proBNP = N-terminal pro-brain natriuretic peptide
NYHA = New York Heart Association
PA = pulmonary artery
PASP = pulmonary artery systolic pressure
RV = right ventricular
RVESA = right ventricular end-systolic area
TAPSE = tricuspid annular plane systolic excursion
TDI = tissue Doppler imaging
TR = tricuspid regurgitation

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included any prior LVEF <40% by echocardiography, clinical event within 6 months of screening that may have reduced LVEF unless post-event echocardiography confirmed LVEF ≥45%, isolated right HF, known pericardial constriction or infiltrative or hypertrophic cardiomyopathy, and hemodynamically significant valvular heart disease or congenital heart disease in the opinion of the investigator. The study was approved by an institutional review committee at each participating site. All patients provided written informed consent.

For quality control purposes and to better characterize the cardiac phenotype in the trial population, the qualifying echocardiogram underwent quantitative analysis at the echocardiography core laboratory at the Brigham and Women's Hospital in a subset of patients (the target was 1,200) from selected centers. All enrolling sites were invited to participate, but participation was at the discretion of each site. A sample size of 1,200 was determined to be large enough to be representative of the trial population on the basis of prior HFpEF clinical trial imaging substudies (9,16). Qualifying echocardiograms were performed within 6 months of the screening visit and were not obtained using a study-specific acquisition protocol. If a qualifying echocardiogram within 6 months of screening was not available, the qualifying echocardiogram was a study performed within the screening epoch, and use of a study-specific imaging protocol was recommended. Consent for review of historical echocardiograms, and for acquisition and review of echocardiograms at the screening visit, was obtained on the main study consent form. Of 1,202 qualifying echocardiograms submitted, 677 (56%) were obtained per study protocol during the screening period prior to administration of study drug, and 525 (44%) were historical studies performed within 6 months of screening. Of these 1,202 studies, image quality was adequate for core laboratory quantification of LVEF in 1,097 (91%), which defines the sample for this analysis.

ECHOCARDIOGRAPHIC METHODS. Echocardiographic studies were sent in digital format to the core laboratory, where quantitative measures were performed in accordance with American Society of Echocardiography (ASE) guidelines, by dedicated analysts blinded to clinical information and randomized treatment assignment. Each measure was performed by the same analyst for all study participants. Intraobserver and interobserver variability for key measures of cardiac structure and function in our laboratory have been previously published (16).

LV volumes and LVEF were derived according to the modified biplane Simpson's rule (17). In cases in which the Simpson's method could not be used because of missing or poor-quality apical views, LVEF was calculated using the Teichholz method (n = 200) (18). LV mass was calculated using the ASE-recommended formula for estimation of LV mass from LV linear dimensions and indexed to body surface area (LV mass index [LVMi]) (17). LA volume was assessed using the modified biplane Simpson's method from apical 2- and 4-chamber views at end-systole and was indexed to body surface area (LA volume index). Peak early diastolic tissue velocity (e′) was measured from the septal and lateral aspects of the mitral annulus. Mitral inflow velocity was assessed using pulsed-wave Doppler from the apical 4-chamber view (19). Mitral regurgitation severity was based on the ratio of mitral regurgitation jet area to LA area from the apical 4- and 2-chamber views as follows: mild, <0.20; moderate, 0.20 to 0.30; moderate to severe, 0.30 to 0.40; and severe, ≥0.40. Aortic stenosis severity was based on peak detected aortic valve velocity as follows: mild, 2.0 to 3.0 m/s; moderate, 3.0 to 4.0 m/s; and severe, ≥4.0 m/s. Right ventricular (RV) functional measures were tricuspid annular plane systolic excursion (TAPSE) and RV fractional area change (FAC), measured using the cavity area at end-diastole and end-systole (20). Peak tricuspid regurgitation (TR) velocity was measured, and pulmonary artery systolic pressure (PASP) was estimated as: $4 \times (\text{peak TR velocity})^2 + 5$. Thresholds for defining abnormal were based on published ASE guidelines (17,19,20).

OUTCOMES. Clinical outcomes included the composite of first HF hospitalization or cardiovascular (CV) death, the composite of total (first and recurrent) HF hospitalizations and CV death (PARAGON-HF primary endpoint), first HF hospitalization alone, and CV death alone. All events were reported by the primary site investigator and were independently adjudicated by a clinical endpoints center, as previously described in detail (14).

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD or as median (interquartile range) as specified. Comparisons of baseline clinical measures between PARAGON-HF patients included (n = 1,097) and not included (n = 3,699) in the echocardiography cohort were performed using the Fisher exact test for categorical variables and Student's *t*-test or the Wilcoxon rank sum test for continuous variables as specified. Measures of cardiac structure and function are described for the overall echocardiography study sample. To more closely estimate

measures of cardiac structure and function representative of the overall trial population, we performed supplemental analyses incorporating inverse probability of attrition weights to account for differences between PARAGON-HF patients included and those not included in the echocardiographic study (Online Appendix) (21).

Multivariable Cox proportional hazards models were used to study the association of echocardiographic measures with the clinical outcomes. Echocardiographic exposures were modeled as continuous and categorical variables (dichotomized into normal and abnormal on the basis of ASE guideline recommendations). Two multivariate Cox models were used on the basis of a priori knowledge: 1) model 1 adjusted for age, sex, region of enrollment, and randomized treatment; 2) model 2 additionally adjusted for log(NT-proBNP), hypertension, diabetes, prior myocardial infarction, AF, prior HF hospitalization, NYHA functional class, estimated glomerular filtration rate, and use of a mineralocorticoid antagonist (22–25). No echocardiographic predictors violated the proportional hazards assumption on the basis of Schoenfeld residuals. For echocardiographic measurements demonstrating robust associations with clinical outcomes in adjusted analysis, the flexible continuous relationship with first HF hospitalization or CV death was further assessed using restricted cubic splines with the number of knots selected to minimize the model Akaike information criteria (3 to 7 knots tested). The relationship between echocardiographic measures and the primary PARAGON-HF endpoint of the composite of the total (first and recurrent) HF hospitalizations or CV death during the follow-up period was assessed using the semiparametric method of Lin, Wei, Yang, and Ying, which is a modified Anderson-Gill method with a robust variance estimator (26). This statistical method was used for the primary PARAGON-HF statistical analysis plan (14,27). It has the benefit of being a recurrent-events model that requires fewer parametric assumptions compared with other approaches to recurrent events, such as the negative binominal model, and is therefore thought to be more robust.

The primary analysis was performed using raw data, even when some patients had missing values. An additional sensitivity analysis was performed using multiple imputation for missing data. Given the arbitrary missing value pattern of the echocardiographic data, we used multiple imputation by chained equations, an iterative imputation procedure (Stata mi impute chained). Imputation was performed for each echocardiographic measure with any missing data and was based on linear regression using 20 baseline clinical variables (Table 1) and the 30 echocardiographic measures as predictor variables and was derived over 40 imputations. A p value <0.05

TABLE 1 Baseline Characteristics of PARAGON-HF Patients Included Compared With Those Not Included in the Echocardiography Study

	In Echocardiography Study (n = 1,097)	Not in Echocardiography Study (n = 3,699)	p Value
Demographics			
Age, yrs	73.7 ± 8.0	72.5 ± 8.5	<0.001
Female	579 (53)	1,900 (51)	0.41
Race/ethnicity			<0.001
White	887 (81)	3,020 (82)	
Asian	159 (15)	448 (12)	
Black or African American	41 (4)	61 (2)	
Other	10 (1)	170 (5)	
Enrollment region			<0.001
North America	324 (30)	235 (6)	
Western Europe	332 (30)	1,058 (29)	
Central Europe	243 (22)	1,472 (40)	
Asia/Pacific	183 (17)	579 (16)	
Latin America	15 (1)	355 (10)	
Comorbidities			
Prior MI	233 (21)	850 (23)	0.23
Ischemic etiology	333 (30)	1,390 (38)	<0.001
Atrial fibrillation	380 (35)	1,172 (32)	0.06
Prior HF hospitalization	506 (46)	1,800 (49)	0.14
Hypertension	1,030 (94)	3,554 (96)	0.002
Diabetes	441 (40)	1,621 (44)	0.033
Obesity	507 (46)	1,851 (50)	0.03
CKD	583 (53)	1,758 (48)	0.001
Stroke	126 (12)	382 (10)	0.26
Examination and laboratory values			
NYHA functional class			0.10
I	41 (4)	96 (3)	
II	833 (76)	2,873 (78)	
III	221 (20)	711 (19)	
IV	2 (0.2)	17 (0.5)	
SBP, mm Hg	129 ± 16	131 ± 15	<0.001
DBP, mm Hg	72 ± 11	75 ± 10	<0.001
Heart rate, beats/min	69 ± 12	71 ± 12	0.003
BMI, kg/m^2	29.9 ± 4.9	30.3 ± 5.0	0.009
eGFR, ml/min/1.73 m^2	60 ± 18	63 ± 19	<0.001
NT-proBNP, pg/ml	918 (485-1,578)	909 (458-1,633)	0.59
Site-reported LVEF, %	58.5 ± 7.7	57.2 ± 7.9	<0.001
Medication use			
Diuretics	1,029 (94)	3,505 (95)	0.22
Mineralocorticoid receptor antagonist	247 (23)	972 (26)	0.012
ACE inhibitor or ARB	894 (82)	3,245 (88)	<0.001
Beta-blocker	858 (78)	2,922 (79)	0.58

Values are mean ± SD, n (%), or median (interquartile range). Between-group comparisons for continuous variables were performed using Student's *t*-test.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CKD = chronic kidney disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PARAGON-HF = Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction; SBP = systolic blood pressure.

TABLE 2 Cardiac Structure and Function in the PARAGON-HF Echocardiography Study

			Abnormal	Definition of Abnormal
LV structure				
LVEDVi, ml/m^2	897	52.8 ± 16.8	136 (15)	>74 (men), >61 (women)
LVESVi, ml/m^2	897	22.2 ± 10.6	225 (25)	>31 (men), >24 (women)
LVEDD, cm	1,037	4.61 ± 0.65	79 (8)	>5.84 (men), >5.22 (women)
LVESD, cm	959	3.29 ± 0.68	267 (28)	>3.98 (men), >3.48 (women)
Septal wall thickness, cm	1,044	1.10 ± 0.24	774 (74)	>1.0 (men), >0.9 (women)
Posterior wall thickness, cm	1,021	0.96 ± 0.20	472 (46)	>1.0 (men); >0.9 (women)
Mean wall thickness, cm	1,016	1.03 ± 0.20	628 (62)	>1.0 (men), >0.9 (women)
LV mass, g	1,015	169.1 ± 56.8	300 (30)	>224 (men), >162 (women)
LV mass index, g/m^2	1,015	87.3 ± 26.5	214 (21)	>115 (men), >95 (women)
RWT	1,019	0.43 ± 0.12	459 (45)	>0.42
LV geometry	1,015			
Normal		–	468 (46)	–
Concentric remodeling		–	333 (33)	–
Concentric hypertrophy		–	124 (12)	–
Eccentric hypertrophy		–	90 (9)	–
LV systolic function				
LVEF, %	1,097	58.6 ± 9.8	294 (27)	<52 (men), <54 (women)
≥50%		–	864 (79)	–
45%–50%		–	109 (10)	–
40%–45%		–	87 (8)	–
35%–40%		–	17 (2)	–
<35%		–	20 (2)	–
TDI septal s′, cm/s	795	5.6 ± 1.4	–	–
LV diastolic function				
E/A ratio	592	1.33 ± 0.73	–	–
E wave, cm/s	964	90.0 ± 27.8	–	–
A wave, cm/s	605	73.5 ± 26.0	–	–
TDI septal e′, cm/s	774	5.8 ± 1.8	590 (76)	<7
TDI septal e′, cm/s	747	7.9 ± 2.5	605 (81)	<10
E/e′, septal	748	16.8 ± 7.3	388 (52)	>15
E/e′, lateral	715	12.6 ± 5.7	262 (37)	>13
Any abnormal E/e′	833	–	442 (53)	–
LA size and function				
LA diameter, cm	962	4.23 ± 0.65	682 (71)	>4.0 (men), >3.8 (women)
LA area, cm^2	698	22.9 ± 5.6	486 (70)	>20
LA volume, ml	978	74.7 ± 29.7	762 (78)	>58 (men), >52 (women)
LA volume index, ml/m^2	978	38.9 ± 15.5	573 (59)	>34
Normal			405 (41)	≤34
Mild			232 (24)	34–41
Moderate			148 (15)	41–48
Severe			193 (20)	>48
Any LA enlargement	1,097	–	906 (83)	–
TDI septal a′, cm/s	496	6.5 ± 2.1	–	–
TDI lateral a′, cm/s	492	7.4 ± 2.8	–	–
Valvular disease				
MR jet area/LA area ratio	908	0.06 (0.00–0.14)	83 (9)	Moderate MR
			28 (3)	More than moderate MR
AV peak velocity, m/s	844	1.4 ± 0.5	86 (10)	Mild AS
			15 (2)	Moderate or greater AS

Continued on the next page

was considered statistically significant. Given the large number of echocardiographic predictors, a Bonferroni-corrected p value of <0.0015 (accounting for 34 echocardiographic predictors) was also considered as a threshold for statistical significance, although this may be overly conservative, as echocardiographic predictors were not independent of one another. All analyses were performed using Stata version 16 (StataCorp, College Station, Texas).

TABLE 2 Continued

			Abnormal	Definition of Abnormal
Pulmonary pressure and right ventricle				
TR velocity, m/s	489	2.67 ± 0.46	151 (31)	>2.90
PASP, mm Hg	489	34 ± 10	124 (25)	≥39
TAPSE, cm	515	1.81 ± 0.42	157 (31)	<1.60
TAPSE/PASP ratio	279	0.57 ± 0.20	–	–
RV FAC, %	620	47.0 ± 9.3	56 (9)	<35
RVEDA, cm^2	620	21.0 ± 5.9	243 (39)	>24 (men), >20 (women)
RVESA, cm^2	620	11.2 ± 4.1	169 (27)	>15 (men), >11 (women)
IVC diameter, cm	303	1.7 ± 0.4	59 (19)	>2.1

Values are n, mean ± SD, n (%), or median (interquartile range), unless otherwise indicated.

a′ = peak late diastolic mitral annular tissue velocity; AS = aortic stenosis; AV = aortic valve; A wave = peak late diastolic transmitral flow velocity; e′ = peak early diastolic mitral annular tissue velocity; E wave = peak early diastolic transmitral flow velocity; IVC = inferior vena cava; LVESD = left ventricular end-systolic dimension; FAC = fractional area change; LA = left atrial; LV = left ventricular; LVEDD = left ventricular end-diastolic dimension; LVEDVi = left ventricular end-diastolic volume indexed to body surface area; LVESD = left ventricular end-systolic dimension; LVESVi = left ventricular end-systolic volume indexed to body surface area; MR = mitral regurgitation; PASP = pulmonary artery systolic pressure; RVEDA = right ventricular end-diastolic area; RVESA = right ventricular end-systolic area; RWT = relative wall thickness; s′ = peak systolic mitral annular tissue velocity; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging; TR = tricuspid regurgitation; other abbreviations as in Table 1.

RESULTS

The average age of the 1,097 PARAGON-HF patients in the echocardiography cohort was 74 ± 8 years, 53% were women, 46% were obese (body mass index ≥30 kg/m^2), and the median NT-proBNP level was 918 pg/ml (interquartile range: 485 to 1,578 pg/ml) (Table 1). Comorbid hypertension, diabetes, prior myocardial infarction, and AF were common; most patients were receiving diuretic agents, beta-blockers, and inhibitors of the renin-angiotensin system (prior to enrollment), and 23% were on mineralocorticoid antagonists at baseline. Compared with PARAGON-HF patients not in the echocardiography cohort, those in the echocardiography cohort were older and more commonly enrolled in North America (Table 1). Modest differences were observed in comorbidity prevalence, but no differences were observed in NYHA functional class or prevalence of prior HF hospitalization.

CARDIAC STRUCTURE AND FUNCTION IN PARAGON-HF. The median LVEF was 58.6 ± 9.8%, with core laboratory LVEFs ≥50% in 79%, 40% to 50% in 18%, and <40% in 3% (Table 2). The mean difference between site-reported and core laboratory-measured LVEF was 0.1 ± 9.3%. The overall prevalence of LV hypertrophy (LVH) on the basis of LVMi was 21%, with a concentric pattern in 11% and an eccentric pattern in 10% of patients. Concentric remodeling was present in an additional 25%. Evidence of LA enlargement, on the basis of LA diameter, area, volume, or indexed volume, was present in 83% patients. Lateral and septal e′ on tissue Doppler imaging (TDI) were reduced in >75% of patients, while E/e′ ratio (either septal or lateral) was elevated in 52%. TR peak velocity was measurable in 489 patients (45% of the echocardiography cohort). The mean velocity was 2.7 ± 0.5 m/s, and velocity was >2.9 m/s in 31% of patients (Table 2). Mean RV end-diastolic area was 21.0 ± 5.9 cm^2 and was enlarged in 39%. RV FAC was reduced in 9%, while TAPSE was abnormal in 31%. Overall, among the 868 participants with TDI data (≥1 of septal or lateral), 96% had 2016 European Society of Cardiology HF guideline echocardiographic criteria for HFpEF (28). Similar findings were observed in supplemental analyses incorporating inverse probability of attrition weights to account for differences between those included and not included in the echocardiography study (Online Table 1) and using multiple imputation for missing echocardiographic data (Online Table 2).

CARDIAC STRUCTURE AND FUNCTION AND TIME TO FIRST HF HOSPITALIZATION OR CV DEATH. During a median follow-up period of 2.8 years, 288 patients in the PARAGON-HF echocardiography study experienced HF hospitalization or CV death (event rate: 9.9 per 100 person-years; 95% confidence interval [CI]: 8.8 to 11.1). In multivariate Cox proportional hazards models adjusted for age, sex, region of enrollment, and randomized treatment assignment (model 1), greater LV wall thickness, LV mass, and LVMi were all associated with heightened risk for HF hospitalization or CV death (Table 3) and remained significantly associated after further adjustment for NT-proBNP, hypertension, diabetes, prior myocardial infarction, AF, prior HF hospitalization, NYHA functional class, and mineralocorticoid receptor antagonist use (model 2). LVEF was not associated with the composite of HF

TABLE 3 Cardiac Structure and Function and Incident HF Hospitalization or Cardiovascular Death in PARAGON-HF

	Dichotomous				Continuous*	
	Event Rate per 100 Person-Years (95% CI)		Model 1	Model 2	Model 1	Model 2
	Normal	Abnormal	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
LV structure						
LVEDVi, ml/m^2	10.3 (8.9–11.7)	12.7 (9.4–17.1)	1.47 (1.05–2.07), p = 0.03	1.28 (0.90–1.83), p = 0.17	1.08 (0.99–1.17), p = 0.07	1.03 (0.95–1.12), p = 0.45
LVESVi, ml/m^2	10.4 (9.0–12.0)	11.1 (8.7–14.2)	1.23 (0.92–1.65), p = 0.16	1.02 (0.75–1.38), p = 0.90	1.16 (1.03–1.31), p = 0.02	1.06 (0.93–1.20), p = 0.39
LVEDD, cm	9.6 (8.5–10.9)	12.9 (8.6–19.2)	1.60 (1.04–2.46), p = 0.03	1.32 (0.85–2.05), p = 0.22	1.04 (0.94–1.15), p = 0.47	0.99 (0.89–1.09), p = 0.77
LVESD, cm	9.9 (8.6–11.4)	10.2 (8.1–12.9)	1.17 (0.88–1.54), p = 0.28	1.11 (0.84–1.48), p = 0.46	1.06 (0.97–1.17), p = 0.21	1.01 (0.92–1.12), p = 0.79
Mean wall thickness, cm	7.9 (6.4–9.8)	11.0 (9.5–12.8)	1.32 (1.02–1.72), p = 0.04	1.36 (1.04–1.78), p = 0.03	1.18 (1.05–1.32), p = 0.005	1.14 (1.02–1.28), p = 0.03
LV mass, g	9.0 (7.7–10.4)	12.0 (9.8–14.8)	1.41 (1.09–1.82), p = 0.009	1.28 (0.98–1.66), p = 0.07	1.07 (1.03–1.12), p = 0.001†	1.05 (1.00–1.10), p = 0.04
LV mass index, g/m^2	8.9 (7.7–10.4)	11.7 (9.2–14.9)	1.40 (1.06–1.85), p = 0.02	1.18 (0.89–1.58), p = 0.25	1.08 (1.04–1.13), p < 0.001†	1.05 (1.00–1.10), p = 0.03
RWT	8.9 (7.5–10.5)	11.1 (9.3–13.1)	1.10 (0.86–1.41), p = 0.45	1.16 (0.90–1.49), p = 0.25	1.06 (0.97–1.17), p = 0.20	1.07 (0.97–1.18), p = 0.18
LV systolic function						
LVEF, %	9.7 (8.4–11.1)	10.5 (8.4–13.1)	1.18 (0.91–1.54), p = 0.22	0.99 (0.75–1.29), p = 0.92	0.99 (0.98–1.00), p = 0.11	1.00 (0.99–1.01), p = 0.66
TDI septal s′, cm/s	–	–			0.89 (0.80–0.99), p = 0.03	0.96 (0.86–1.08), p = 0.50
LV diastolic function						
E-wave, cm/s	–	–	–	–	1.01 (1.01–1.01), p < 0.001†	1.01 (1.00–1.01), p < 0.001†
A-wave, cm/s	–	–	–	–	1.01 (1.00–1.01), p = 0.05	1.01 (1.00–1.02), p = 0.007
E/A ratio	–	–	–	–	1.09 (0.89–1.35), p = 0.40	0.98 (0.77–1.26), p = 0.89
TDI septal e′, cm/s	6.9 (5.0–9.6)	11.1 (9.6–12.9)	1.61 (1.12–2.32), p = 0.01	1.39 (0.95–2.03), p = 0.09	0.87 (0.80–0.94), p = 0.001†	0.90 (0.83–0.99), p = 0.03
TDI lateral e′, cm/s	8.4 (6.0–11.8)	10.3 (8.8–12.0)	1.20 (0.83–1.75), p = 0.33	1.10 (0.75–1.63), p = 0.62	0.93 (0.88–0.99), p = 0.02	0.95 (0.89–1.01), p = 0.10
E/e′, septal	6.2 (4.9–8.0)	13.8 (11.7–16.4)	2.09 (1.53–2.84), p < 0.001†	1.77 (1.28–2.46), p = 0.001†	1.06 (1.04–1.07), p < 0.001†	1.04 (1.03–1.06), p < 0.001†
E/e′, lateral	7.5 (6.2–9.2)	14.2 (11.6–17.4)	1.85 (1.38–2.48), p < 0.001†	1.56 (1.15–2.11), p = 0.004	1.06 (1.04–1.08), p < 0.001†	1.04 (1.02–1.07), p < 0.001†
LA size and function						
LA diameter, cm	10.0 (8.0–12.5)	9.9 (8.5–11.4)	1.01 (0.77–1.32), p = 0.96	0.88 (0.67–1.17), p = 0.39	1.05 (0.87–1.27), p = 0.63	0.96 (0.78–1.19), p = 0.72
LA area, cm^2	9.8 (7.6–12.8)	10.6 (8.9–12.5)	1.03 (0.75–1.42), p = 0.83	0.89 (0.64–1.24), p = 0.51	0.95 (0.84–1.09), p = 0.49	0.93 (0.80–1.08), p = 0.32
LA volume, ml	8.4 (6.4–11.1)	10.6 (9.2–12.1)	1.23 (0.90–1.68), p = 0.20	1.09 (0.79–1.51), p = 0.61	0.98 (0.90–1.07), p = 0.61	0.97 (0.88–1.07), p = 0.57
LA volume index, cm/cm^2	9.6 (7.8–11.8)	9.9 (8.4–11.7)	0.96 (0.75–1.24), p = 0.77	0.90 (0.69–1.17), p = 0.43	0.99 (0.91–1.07), p = 0.77	0.98 (0.89–1.08), p = 0.70
Any LA enlargement	10.0 (7.6–13.1)	9.9 (8.7–11.3)	0.97 (0.71–1.31), p = 0.83	0.86 (0.63–1.18), p = 0.34		
TDI septal a′, cm/s	–	–			0.89 (0.82–0.97), p = 0.009	0.95 (0.87–1.03), p = 0.22
TDI lateral a′, cm/s	–	–			0.89 (0.84–0.95), p = 0.001†	0.93 (0.87–1.00), p = 0.05

Continued on the next page

hospitalization or CV death. Similarly, no measure of LA size was associated with this composite endpoint. Similar findings were observed in both patients with and those without histories of AF at randomization, with the exception of a nominal association of LA volume with HF hospitalization or CV death among patients without AF (Online Table 3). In contrast, multiple Doppler-based diastolic measures were robustly associated with incident HF hospitalization or CV death (**Table 3**). Higher E-wave velocity, lower

TABLE 3 Continued

	Dichotomous				Continuous*	
	Event Rate per 100 Person-Years (95% CI)		Model 1	Model 2	Model 1	Model 2
	Normal	Abnormal	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Valvular disease						
MR jet area/LA area ratio	–	–			1.09 (1.03–1.16), p = 0.006	1.05 (0.99–1.12), p = 0.13
Moderate or greater MR	10.3 (9.1–11.8)	10.9 (7.6–15.4)	1.07 (0.73–1.57), p = 0.71	1.00 (0.68–1.48), p = 0.99	–	–
Peak AV velocity	–	–			1.28 (1.15–1.44), p < 0.001†	1.28 (1.14–1.44), p < 0.001†
Mild or greater AS	8.5 (7.3–9.9)	18.6 (13.9–25.0)	1.98 (1.42–2.77), p < 0.001†	1.86 (1.32–2.63), p < 0.001†	–	–
Pulmonary pressure and right ventricle						
TR velocity, m/s	7.2 (5.7–9.1)	15.2 (11.7–19.7)	2.06 (1.45–2.94), p < 0.001†	2.26 (1.56–3.27), p < 0.001†	1.66 (1.37–2.00), p < 0.001†	1.61 (1.33–1.95), p < 0.001†
PASP, mm Hg	7.1 (5.7–9.0)	17.4 (13.3–22.9)	2.42 (1.69–3.47), p < 0.001†	2.58 (1.77–3.77), p < 0.001†	1.55 (1.34–1.80), p < 0.001†	1.51 (1.29–1.76), p < 0.001†
TAPSE, cm	7.3 (5.8–9.2)	12.4 (9.4–16.3)	1.61 (1.12–2.32), p = 0.01	1.34 (0.90–1.99), p = 0.15	0.55 (0.35–0.86), p = 0.009	0.65 (0.41–1.04), p = 0.07
TAPSE/PASP ratio (per 0.01 units)	–	–			0.97 (0.96–0.99), p < 0.001†	0.97 (0.96–0.99), p < 0.001†
RVFAC, %	9.6 (8.2–11.3)	11.2 (7.0–18.0)	0.98 (0.58–1.65), p = 0.93	0.95 (0.54–1.67), p = 0.86	0.99 (0.97–1.00), p = 0.13	0.99 (0.97–1.01), p = 0.28
RVEDA, cm^2	8.3 (6.7–10.2)	12.3 (9.8–15.3)	1.53 (1.12–2.10), p = 0.008	1.52 (1.10–2.10), p = 0.01	1.05 (1.02–1.07), p = 0.001†	1.04 (1.01–1.07), p = 0.004
RVESA, cm^2	8.2 (6.8–10.0)	14.3 (11.1–18.4)	1.94 (1.40–2.69), p < 0.001†	1.76 (1.26–2.46), p = 0.001†	1.07 (1.03–1.11), p < 0.001†	1.06 (1.02–1.10), p = 0.001†
IVC diameter, cm	9.7 (7.6–12.4)	13.5 (8.9–20.5)	1.23 (0.74–2.03), p = 0.43	1.40 (0.83–2.39), p = 0.21	1.34 (0.84–2.15), p = 0.22	1.38 (0.83–2.3), p = 0.22

*HR estimates for continuous measures are per 10 ml/m^2 for LVEDVi and LVESVi, per 0.5 cm for LVEDD and LVESD, per 0.2 cm for IVS and PW thickness, per 20 g for LV mass, per 10 g/m^2 for LVMi, per 0.10 units for RWT, per 5 cm^2 for LA area, per 20 ml for LA volume, per 10 ml/m^2 for LA volume index, per 0.05 units for MR jet area/LA area ratio, per 0.5 m/s for peak aortic valve velocity, per 0.5 m/s for TR velocity, and per 10 mm Hg for PASP. †Statistically significant after Bonferroni correction for multiple testing at p < 0.0015. Refer to Table 2 for criteria used to dichotomize predictor variables. Model 1 adjusted for age, sex, region of enrollment, and randomized treatment; model 2 additionally adjusted for log(NT-proBNP), hypertension, diabetes, prior MI, atrial fibrillation, prior HF hospitalization, NYHA functional class, eGFR, and use of a mineralocorticoid antagonist.

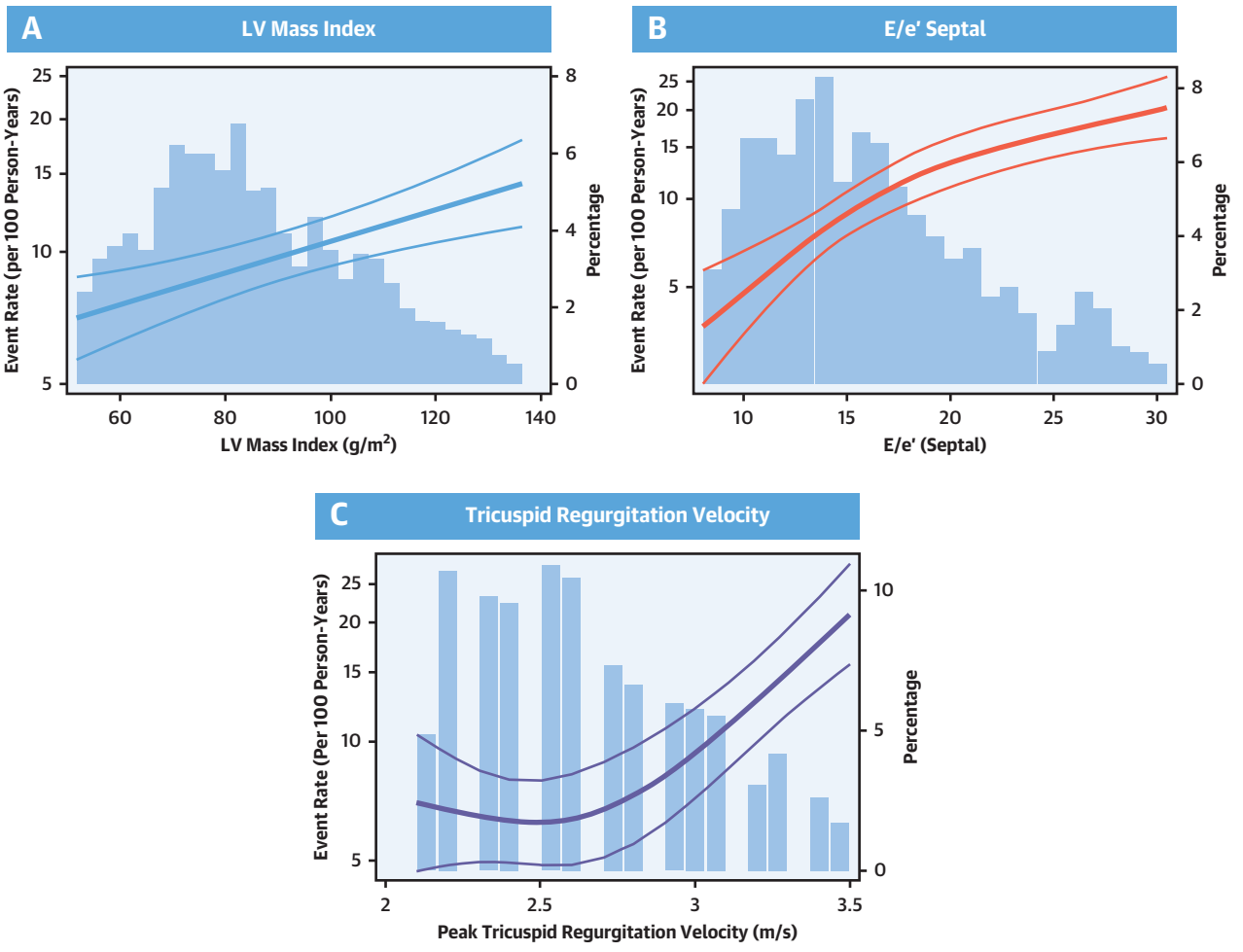
CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

TDI septal e′, and higher septal and lateral E/e′ ratios were each associated with higher risk for the composite endpoint in fully adjusted models. Higher peak aortic valve velocity, and mild or greater stenosis, were also independently associated with this composite, whereas mitral regurgitation severity was not. Higher E-wave velocity, higher septal and lateral E/e′ ratios, and higher peak aortic valve velocity remained independently predictive at a Bonferroni-corrected significance level of p < 0.0015.

High TR velocity was associated with HF hospitalization or CV death in fully adjusted models. This association was nonlinear, with greater risk at higher TR velocity observed at values >~2.6 m/s (Figure 1). Among 360 patients with complete data on LVMi, E/e′, and TR velocity, echocardiographic abnormalities demonstrated appreciable overlap and were additive with respect to risk for incident HF hospitalization or CV death (Figure 2). Lower TAPSE, indicative of worse RV function, was associated with greater risk (model 1), but not in fully adjusted models. RV-pulmonary artery (PA) coupling, assessed as the TAPSE/PASP ratio, was available in 279 patients and was independently and linearly associated with incident HF hospitalization or CV death. Larger RV size, reflected in RV end-diastolic area and RV end-systolic area (RVESA), was also linearly associated with increased risk in fully adjusted models. Higher TR velocity, lower TAPSE/PASP ratio, and larger RVESA remained independently predictive at a Bonferroni-corrected significance level of p < 0.0015.

Similar findings were observed in analyses using multiple imputation to account for missing echocardiographic data (Online Table 4). Similar echocardiographic associations were observed for the endpoint of first HF hospitalization alone (Online Table 5), with the exception that greater mitral regurgitation severity was also predictive of HF hospitalization (hazard ratio for ratio of mitral regurgitation jet area to LA area per 0.05 units: 1.08; 95% CI: 1.01 to 1.16; p = 0.03). LV wall thickness and mass were also predictive of CV death alone,

FIGURE 1 **Continuous Associations Between Key Echocardiographic Measures and Incident First HF Hospitalization or CV Death**

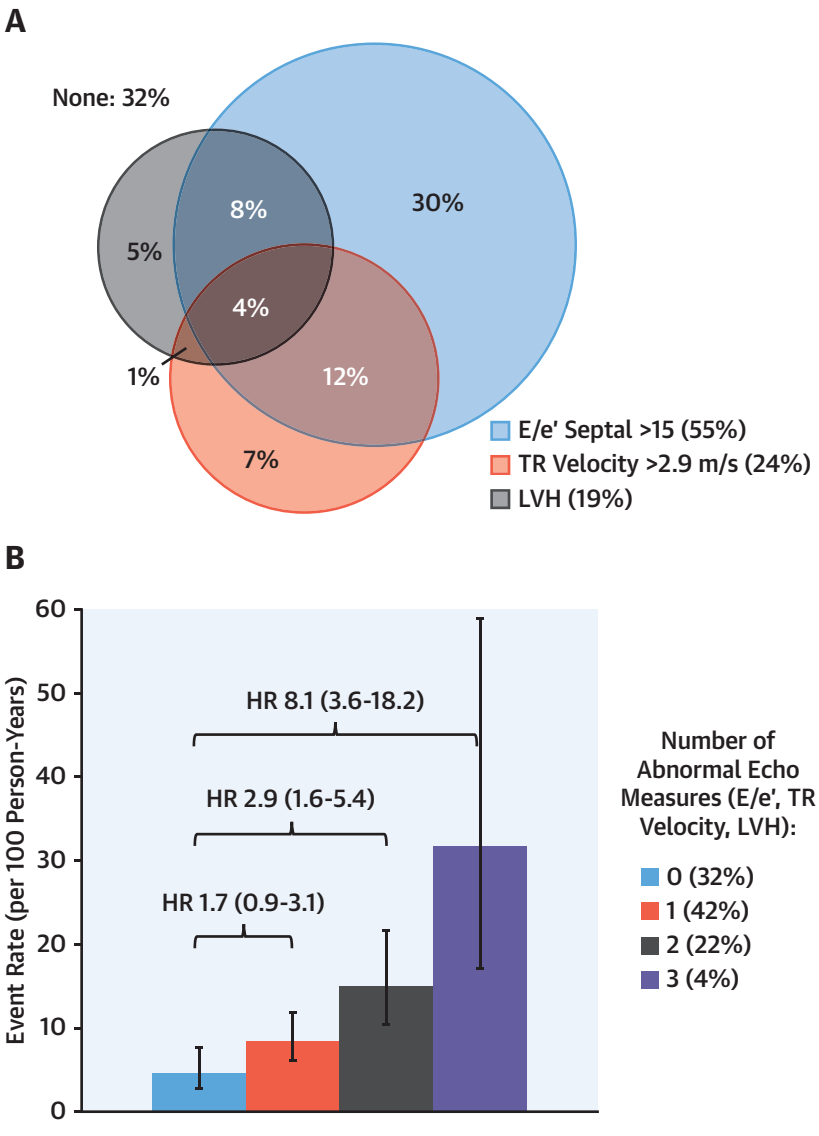


Restricted cubic spline analysis demonstrating the continuous association of **(A)** left ventricular (LV) mass index (n = 1,015; p = 0.001; p for nonlinearity = 0.35), **(B)** septal E/e′ ratio (n = 748; p < 0.0001; p for nonlinearity = 0.02), and **(C)** tricuspid regurgitation jet velocity (n = 489; p < 0.0001; p for nonlinearity = 0.007) with incidence rate of heart failure (HF) hospitalization or cardiovascular (CV) death. All models are adjusted for age and sex. LV mass index demonstrated a linear association with outcomes, while the associations of E/e′ ratio and tricuspid regurgitation jet velocity with incident HF hospitalization or CV death were significantly nonlinear.

although the magnitude of effect appeared greater than that for HF alone (Online Table 6). Greater relative wall thickness was also associated with CV death in fully adjusted models (hazard ratio per 0.10-U increase: 1.34; 95% CI: 1.10 to 1.64; p = 0.004). Greater peak aortic valve velocity, higher PASP, larger RVESA, and lower TAPSE were all also predictive of CV death. However, in contrast to HF hospitalization, E wave, TDI e′, and E/e′ ratio were not predictive.

CARDIAC STRUCTURE AND FUNCTION AND TOTAL HF HOSPITALIZATIONS OR CV DEATH. During the same follow-up period (median 2.8 years), 570 total HF hospitalizations (first and recurrent) or CV deaths occurred. Compared with first HF hospitalization or CV death, similar associations between LV structural measures (wall thickness, mass) and Doppler-based diastolic measures (E wave, TDI e′, E/e′ ratio) were observed with total HF hospitalizations or CV death (the PARAGON-HF primary endpoint) but were more statistically robust (**Table 4**). In addition to higher peak aortic valve velocity, greater mitral regurgitation severity was also predictive of this endpoint. In addition to significant associations with higher TR velocity, larger RV size, and worse TAPSE/PASP ratio, larger inferior vena cava maximal diameter, a measure of systemic venous congestion, was also associated with total HF hospitalizations or CV death in

FIGURE 2 Coexistence of Abnormalities of LV Mass Index, E/e′ Ratio, and Tricuspid Regurgitation Jet Velocity, and Their Additive Prognostic Relevance for Incident First HF Hospitalization or CV Death



Analysis of the prevalence and prognostic relevance of concomitant abnormalities of left ventricular (LV) mass index, E/e′ ratio, and tricuspid regurgitation (TR) jet velocity among 360 patients with all 3 measures available. **(A)** Venn diagram demonstrating the overlap of these abnormalities, demonstrating frequent overlap of LV hypertrophy (LVH) and pulmonary hypertension with abnormal E/e′ ratio. **(B)** Event rates (per 100 person-years) of incident heart failure (HF) hospitalization or cardiovascular (CV) death on the basis of the number of abnormal echocardiographic findings (LVH, E/e′, or abnormal TR jet velocity), demonstrating their additive risk. HR = hazard ratio.

fully adjusted models. No associations were observed with measures of LA size. Mean wall thickness, LVMi, peak E-wave velocity, E/e′ ratio, peak aortic valve velocity, peak TR velocity, TAPSE/PASP ratio, and RVESA remained independently predictive of total HF hospitalizations or CV death at a Bonferroni-corrected significance level of $p < 0.0015$. Similar findings were observed in sensitivity analyses using multiple imputation (Online Table 4).

DISCUSSION

Among 1,097 patients enrolled in the PARAGON-HF echocardiography study, we observed a high

CENTRAL ILLUSTRATION **Cardiac Structure and Function in Heart Failure With Preserved Ejection Fraction**

	LV and LA structure		*Left and Right Heart Pressures*		*Clinical Outcomes*
	LV mass (g)	LA area (cm^2)	E/e'	RVSP (mm Hg)	Event Rate
PARAGON-HF	169 ± 57*	23 ± 6	13 ± 6*	34 ± 10*	10 [9-11]
TOPCAT	223 ± 71*	20 ± 6*	12 ± 6*	38 ± 11*	12 [10-14]
IPRESERVE	164 ± 48*	23 ± 6*	10 ± 5*	37 ± 13*	-

Higher value | Lower value

Shah, A.M. et al. J Am Coll Cardiol. 2019;74(23):2858–73.

Echocardiography in heart failure with preserved ejection fraction (HFpEF) clinical trials highlighting the high prevalence of elevated left and right heart pressures in PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction) and the heterogeneity of the cardiac phenotype in HFpEF. Table of mean values for left ventricular (LV) mass, left atrial (LA) area, E/e′ ratio, and right ventricular systolic pressure (RVSP) in PARAGON-HF and echocardiography substudies of 2 other phase 3 HFpEF clinical trials. PARAGON-HF was characterized by left atrial enlargement and elevated markers of left and right heart pressures. This table also highlights the structural heterogeneity across these HFpEF studies, despite similarly elevated markers of cardiac pressures and clinical event rates. Clinical outcome is time to first heart failure hospitalization or cardiovascular death. Event rate is per 100 person-years. Pulmonary artery systolic pressure in PARAGON-HF and TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) assumes right atrial pressure of 5 mm Hg and in I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction) assumes right atrial pressure of 10 mm Hg. *Measure prognostic of adverse outcomes.

prevalence of LA enlargement, Doppler-based indices of diastolic dysfunction, and pulmonary hypertension (Central Illustration). Abnormalities of LV structure were present in 46%, with LVH in 21%. After accounting for demographics, randomized treatment, NT-proBNP, and clinical comorbidities, higher LVMi, higher E/e′ (indicative of higher filling pressure), higher pulmonary pressure, worse RV-PA coupling, and larger RV size were each independently associated with risk for HF hospitalization or CV death, whereas LA size was not. Higher E/e′ ratio, higher pulmonary pressure, worse RV-PA coupling, and larger RV size remained significant after accounting for multiple testing. Together, these findings suggest a high prevalence of elevated LV filling pressure, diastolic dysfunction, pulmonary hypertension, and RV dysfunction in PARAGON-HF and identify many of these as independent risk factors for HF hospitalization or CV death in HFpEF.

The phase 2 PARAMOUNT (Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction) trial investigated the impact of sacubitril-valsartan compared with valsartan alone on NT-proBNP and echocardiographic measures in patients with HFpEF and found a significant reduction in NT-proBNP at 12 weeks and LA volume index at 36 weeks (29). Measures of cardiac structure and function were generally comparable in PARAGON-HF compared with PARAMOUNT, with the exception of modestly greater LV wall thickness, smaller LV size, and larger LA volume in PARAGON-HF (Table 4). These differences are likely due to the requirement for either increased LV wall thickness or LA enlargement (site determined) for enrollment in PARAGON-HF but not in PARAMOUNT. Interestingly, E/e′ ratio was similarly elevated in both studies.

LV structural remodeling was present in approximately half of patients in the PARAGON-HF echocardiography substudy. LV mass and prevalence of LVH were generally lower in PARAGON-HF compared with participants in with HFpEF in community-based cohorts (42% to 75%) (30-33) and contemporary hospital-based HFpEF registries (~60%) (Online Table 7) (34-36). Furthermore, of the 21% of patients with LVH, the pattern of hypertrophy was concentric in 11% and eccentric in 10%. Although the presence of eccentric hypertrophy is perhaps unexpected, this

TABLE 4 Cardiac Structure and Function and Risk for Total (First and Recurrent) HF Hospitalization and CV Death in PARAGON-HF

	Dichotomous		Continuous*	
	Model 1	Model 2	Model 1	Model 2
	HR (95% CI)	HF (95% CI)	HR (95% CI)	HR (95% CI)
LV structure				
LVEDVi, ml/m^2	1.58 (1.25–1.99), p < 0.001†	1.43 (1.12–1.82), p = 0.005	1.10 (1.04–1.16), p = 0.001†	1.05 (0.94–1.17), p = 0.40
LVESVi, ml/m^2	1.40 (1.15–1.72), p = 0.001†	1.15 (0.94–1.42), p = 0.18	1.20 (1.10–1.30), p < 0.001†	1.08 (0.99–1.18), p = 0.07
LVEDD, cm	1.41 (1.05–1.91), p = 0.02	1.07 (0.78–1.46), p = 0.66	1.12 (1.05–1.21), p = 0.001†	1.04 (0.97–1.12), p = 0.25
LVESD, cm	1.30 (1.07–1.57), p = 0.008	1.19 (0.98–1.45), p = 0.08	1.16 (1.08–1.24), p < 0.001†	1.08 (1.01–1.15), p = 0.02
Mean wall thickness, cm	1.36 (1.13–1.65), p = 0.001†	1.35 (1.11–1.64), p = 0.002	1.18 (1.09–1.28), p < 0.001†	1.16 (1.07–1.26), p = 0.001†
LV mass, g	1.65 (1.39–1.97), p < 0.001†	1.44 (1.20–1.73), p < 0.001†	1.09 (1.06–1.12), p < 0.001†	1.07 (1.03–1.10), p < 0.001†
LV mass index, g/m^2	1.40 (1.16–1.70), p = 0.001†	1.18 (0.96–1.43), p = 0.11	1.11 (1.07–1.14), p < 0.001†	1.08 (1.04–1.11), p < 0.001†
RWT	0.99 (0.83–1.18), p = 0.89	1.06 (0.89–1.27), p = 0.51	1.03 (0.96–1.10), p = 0.43	1.05 (0.98–1.13), p = 0.15
LV systolic function				
LVEF, %	1.14 (0.94–1.37), p = 0.18	0.93 (0.77–1.12), p = 0.45	0.99 (0.97–1.01), p = 0.28	1.00 (0.99–1.01), p = 0.97
TDI septal s′, cm/s	–	–	0.87 (0.81–0.94), p < 0.001	0.97 (0.89–1.05), p = 0.42
LV diastolic function				
E wave, cm/s	–	–	1.01 (1.01–1.01), p < 0.001†	1.01 (1.01–1.01), p < 0.001†
A wave, cm/s	–	–	1.00 (1.00–1.01), p = 0.04	1.01 (1.00–1.01), p = 0.002
E/A ratio	–	–	1.22 (1.06–1.41), p = 0.006	1.06 (0.90–1.26), p = 0.47
TDI septal e′, cm/s	2.05 (1.56–2.69), p < 0.001†	1.57 (1.18–2.09), p = 0.002	0.84 (0.79–0.89), p < 0.001†	0.90 (0.85–0.96), p = 0.002
TDI lateral e′, cm/s	1.25 (0.96–1.63), p = 0.10	1.09 (0.82–1.43), p = 0.56	0.91 (0.87–0.94), p < 0.001†	0.94 (0.90–0.98), p = 0.007
E/e′, septal	2.68 (2.13–3.38), p < 0.001†	2.02 (1.59–2.59), p < 0.001†	1.05 (1.04–1.06), p < 0.001†	1.04 (1.03–1.05), p < 0.001†
E/e′, lateral	2.35 (1.91–2.89), p < 0.001†	1.79 (1.45–2.22), p < 0.001†	1.06 (1.05–1.07), p < 0.001†	1.04 (1.02–1.05), p < 0.001†
LA size and function				
LA diameter, cm	1.32 (1.08–1.62), p = 0.007	1.11 (0.90–1.37), p = 0.32	1.11 (0.97–1.27), p = 0.12	1.01 (0.87–1.18), p = 0.86
LA area, cm^2	1.10 (0.88–1.39), p = 0.40	0.91 (0.72–1.16), p = 0.44	0.97 (0.88–1.06), p = 0.48	0.92 (0.83–1.03), p = 0.15
LA volume, ml	1.19 (0.95–1.50), p = 0.13	0.98 (0.78–1.24), p = 0.87	0.98 (0.92–1.04), p = 0.53	0.96 (0.90–1.03), p = 0.31
LA volume index, cm/cm^2	1.03 (0.86–1.23), p = 0.74	0.95 (0.79–1.15), p = 0.61	1.00 (0.94–1.06), p = 0.91	0.98 (0.92–1.05), p = 0.59
Any LA enlargement	1.14 (0.91–1.45), p = 0.26	0.97 (0.77–1.24), p = 0.83	–	–
TDI septal a′, cm/s	–	–	0.88 (0.83–0.93), p < 0.001†	0.93 (0.88–1.00), p = 0.04
TDI lateral a′, cm/s	–	–	0.87 (0.83–0.91), p < 0.001†	0.91 (0.87–0.96), p < 0.001†
Valvular disease				
MR jet area/LA area ratio			1.11 (1.06–1.16), p < 0.001†	1.06 (1.01–1.11), p = 0.01
Moderate or greater MR	1.28 (0.98–1.66), p = 0.067	1.14 (0.87–1.49), p = 0.35		
Peak AV velocity			1.3 (1.21–1.40), p < 0.001†	1.28 (1.18–1.39), p < 0.001†
Mild or greater AS	2.00 (1.61–2.50), p < 0.001†	1.83 (1.45–2.30), p < 0.001†		
Pulmonary pressure and right ventricle				
TR velocity, m/s	2.43 (1.90–3.10), p < 0.001†	2.38 (1.85–3.08), p < 0.001†	1.67 (1.48–1.88), p < 0.001†	1.56 (1.38–1.77), p < 0.001†
PASP, mm Hg	3.02 (2.36–3.87), p < 0.001†	2.86 (2.21–3.70), p < 0.001†	1.51 (1.38–1.66), p < 0.001†	1.44 (1.30–1.59), p < 0.001†
TAPSE, cm	1.70 (1.33–2.17), p < 0.001†	1.30 (1.00–1.70), p = 0.05	0.69 (0.52–0.93), p = 0.02	0.90 (0.67–1.20), p = 0.47
TAPSE/PASP ratio (per 0.01 units)	–		0.98 (0.97–0.99), p < 0.001†	0.98 (0.97–0.99), p < 0.001†
RVFAC, %	0.95 (0.65–1.38), p = 0.78	0.98 (0.66–1.47), p = 0.93	0.98 (0.97–0.99), p = 0.006	0.99 (0.97–1.00), p = 0.06
RVEDA, cm^2	1.34 (1.08–1.68), p = 0.009	1.29 (1.03–1.62), p = 0.03	1.04 (1.02–1.06), p < 0.001†	1.03 (1.01–1.05), p = 0.003
RVESA, cm^2	1.86 (1.48–2.33), p < 0.001†	1.64 (1.29–2.07), p < 0.001†	1.06 (1.04–1.09), p < 0.001†	1.05 (1.03–1.08), p < 0.001†
IVC maximal diameter, cm	1.54 (1.11–2.14), p = 0.01	1.82 (1.28–2.58), p = 0.001†	1.41 (1.02–1.95), p = 0.038	1.55 (1.09–2.20), p = 0.01

*HR estimates for continuous measures are per 10 ml/m^2 for LVEDVi and LVESVi, per 0.5 cm for LVEDD and LVESD, per 0.2 cm for IVS and PW thickness, per 20 g for LV mass, per 10 g/m^2 for LVMi, per 0.10 units for RWT, per 5 cm^2 for LA area, per 20 ml for LA volume, per 10 ml/m^2 for LA volume index, per 0.05 units for MR jet area/LA area ratio, per 0.5 m/s for peak aortic valve velocity, per 0.5 m/s for TR velocity, and per 10 mm Hg for PASP. †Statistically significant after Bonferroni correction for multiple testing at p < 0.0015. Refer to Table 2 for criteria used to dichotomize predictor variables. Model 1 adjusted for age, sex, region of enrollment, and randomized treatment; model 2 additionally adjusted for log(NT-proBNP), hypertension, diabetes, prior MI, atrial fibrillation, prior HF hospitalization, NYHA class, eGFR, and use of a mineralocorticoid antagonist.

Abbreviations as in Tables 1 to 3.

finding is consistent with a prevalence of 16% among HFpEF participants in the Olmsted County cohort and 12% in the Northwestern HFpEF Registry (30,36). However, the prevalence of concentric hypertrophy was appreciably lower than that reported in other community-based and hospital-based HFpEF cohorts (26% to 73%) (Online Table 5). This is particularly intriguing given the comparable degree of elevation

TABLE 5 Cardiac Structure and Function in PARAGON-HF Compared With the Phase 2 PARAMOUNT Trial and Echocardiographic Substudies of Other Phase 3 HFpEF Clinical Trials

	PARAGON-HF (N = 1,097)	PARAMOUNT (29) (N = 292)	TOPCAT Americas (16) (N = 654)	I-PRESERVE (9) (N = 745)	CHARMES (44) (N = 312)	PEP-CHF (45) (N = 850)
Key inclusion criteria	LVEF ≥45%, elevated NT-proBNP, and LVH or LAE	LVEF ≥45%, elevated NT-proBNP	LVEF ≥45% HF hospitalization or elevated BNP/NT-proBNP	LVEF ≥45% NSR on echocardiography	LVEF >40%	LVEF >40% DHF by clinical, echocardiographic criteria
Age, yrs	73.7 ± 8.0	70.6 ± 9.1	71.2 ± 9.9	72 ± 7	66 ± 11	75 (72-79)
Female	53	56	48	62	34	56
LV structure						
LVEDD, cm	4.61 ± 0.65	4.64 ± 0.48	4.80 ± 0.57	4.8 ± 0.6	5.4 ± 0.7	4.6 (4.2-5.1)
LVESD, cm	3.29 ± 0.68	2.99 ± 0.70	3.37 ± 0.49	3.2 ± 0.7	3.6 ± 0.7	NA
LVEDVi, ml/m^2	52.8 ± 16.8	61.4 ± 15.4	47.4 ± 14.1	49 ± 14	NA	NA
LVESVi, ml/m^2	22.2 ± 10.6	26.5 ± 10.4	19.4 ± 8.6	18 ± 9	NA	NA
MWT, cm	1.03 ± 0.20	0.91 ± 0.16	1.19 ± 0.21	0.93 ± 0.15	NA	1.3 (1.2-1.5)
LV mass, g	169 ± 57	148 ± 43	223 ± 71	164 ± 48	237 ± 91	NA
LV mass index, g/m^2	87 ± 27	79.1 ± 22.2	110 ± 31	NA	117 ± 42	NA
Hypertrophy	21	14	50	29	NA	NA
RWT	0.43 ± 0.12	0.38 ± 0.08	0.49 ± 0.11	0.40 ± 0.08	NA	NA
Concentric form of remodeling	45	21	79	54	NA	NA
LV geometry						
Normal	46	72	15	46	NA	NA
Concentric remodeling	33	14	36	25	NA	NA
Concentric hypertrophy	12	7	43	29	NA	NA
Eccentric hypertrophy	9	7	6	0	NA	NA
LV systolic function						
LVEF, %	58.6 ± 9.8	57.7 ± 7.9	59.6 ± 7.8	64 ± 9	50, 18-65	65 (56-66)
LV diastolic function						
LAVi, ml/m^2	38.9 ± 15.5	35.9 ± 13.5	31.1 ± 13.4	–	41.3 ± 14.7	NA
LA area, cm^2	22.9 ± 5.6	21 ± 5	20.2 ± 5.6	23 ± 6	NA	NA
LA diameter, cm	4.2 ± 0.7	3.7 ± 0.5	4.4 ± 0.6	NA	NA	4.5 (4.1-4.8)
E/A ratio	1.33 ± 0.72	1.1 ± 0.62	1.35 ± 0.73	1.05 ± 0.74	1.1 ± 0.7	0.7 (0.6-0.9)
TDI septal E′, cm/s	5.8 ± 1.8	5.8 ± 2.0	6.4 ± 2.4	7.2 ± 2.9	NA	NA
TDI lateral E′, cm/s	7.9 ± 2.5	7.5 ± 2.8	8.5 ± 3.5	9.1 ± 3.4	NA	NA
E/E′ ratio, septal	16.8 ± 7.3	15.9 ± 7.3	16.4 ± 7.2	–	NA	NA
E/E′ ratio, lateral	12.6 ± 5.7	12.7 ± 7.4	12.4 ± 6.0	10.0 ± 4.5	NA	NA
TR velocity, m/s	2.7 ± 0.5	2.5 ± 0.4	2.8 ± 0.5	37 ± 13 (RVSP)	NA	NA

Values are mean ± SD, median (interquartile range), or %.

BNP = brain natriuretic peptide; CHARMES = Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity Echocardiographic Substudy; I-PRESERVE = Irbesartan in Heart Failure With Preserved Ejection Fraction; LAE = left atrial enlargement; LAVi = left atrial volume indexed to body surface area; LVH = left ventricular hypertrophy; MWT = mean wall thickness; NA = not applicable; NSR = normal sinus rhythm; PARAMOUNT = Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction; PEP-CHF = Perindopril in Elderly People With Chronic Heart Failure; RVSP = right ventricular systolic pressure; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist; other abbreviations as in Tables 1 and 2.

in E/e′ ratio and LA size, although data on these measures are limited in most epidemiological studies.

Measures of cardiac structure and function in PARAGON-HF were generally similar to those reported in the echocardiography substudy of the I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction) trial (9), particularly with respect to LV mass and LVH prevalence, LA area, E/e′ ratio, and estimated PASP (Table 5). In contrast, appreciable differences were present compared with patients with HFpEF in the echocardiography substudy of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial (16). Most striking are differences in structure, with greater LV wall thickness, mass, LVH prevalence, and concentricity observed in TOPCAT but substantially lower LA volume index. Despite this, E/e′ ratio and estimated PASP were similar between studies. Event rates were also similar between patients in the TOPCAT Americas (11.7; 95% CI: 10.3 to 13.5) and PARAGON-HF (9.9 per 100 person-years; 95% CI: 8.8 to 11.1) echocardiography substudies. Importantly, quantitative image analysis for both the TOPCAT and PARAGON-HF echocardiography studies was performed in the same imaging core laboratory, making measurement variability an unlikely contributor to these between study differences. Several factors likely do contribute to these differences in

cardiac structure and function among HFpEF clinical trials, the most prominent being differences in trial inclusion criteria. Although these trials uniformly included patients with HF with LVEFs ≥45%, inclusion criteria in PARAGON-HF included a requirement for elevation in natriuretic peptides and echocardiographic abnormalities (increased LV wall thickness or LA enlargement), which were only variably included for other trials (**Table 5**). Another potential contributor is differences in study recruitment locations. Although the reasons are unclear, the comparable elevations in filling pressure (reflected in E/e′ ratio) and clinical event rates observed across trials despite diverse alterations in LV and LA structure highlights the phenotypic and pathophysiologic heterogeneity of the HFpEF syndrome.

Consistent with prior studies (9,10,36), greater LV wall thickness and mass, higher E/e′ ratio and estimated PASP, worse RV function, and greater RV size were all associated with heightened risk for HF hospitalization or CV death. After accounting for clinical risk factors and NT-proBNP, higher LVMi, E/e′, PASP, and RV size remained independently predictive. These findings were concordant for incident HF hospitalization alone and for the composite of total HF hospitalizations or CV death (the PARAGON-HF trial primary endpoint). Greater LVMi, E/e′ ratio, and PASP are routinely quantified in clinical echocardiography laboratories. They have been consistently independently prognostic of HF hospitalization and CV death in HFpEF clinical trials and epidemiological cohort studies, supporting their use to further risk-stratify patients with HFpEF in clinical practice. Notably, differential associations were observed with first HF hospitalization, CV death, and total hospitalizations or CV death. LV structural abnormalities, higher pulmonary pressure, and worse RV function were risk factors for both HF hospitalization and CV death, while Doppler-based diastolic measures (E wave, TDI e′, and E/e′ ratio) were most strongly associated with risk for HF hospitalization, and systemic venous congestion (reflected in inferior vena cava diameter) was particularly relevant for risk for recurrent HF hospitalizations.

RV dysfunction is now recognized as an important risk factor for adverse outcomes in patients with HFpEF (37), although the reported prevalence of RV dysfunction varies widely (38). In PARAGON-HF, TAPSE was abnormal in approximately one-third of patients, while RV FAC was abnormal in <10%, similar to a prior report from TOPCAT. The independent prognostic value of worse RV-PA coupling (reflected in the TAPSE/PASP ratio) and large RV size (RV end-diastolic area, RVESA) further support an important independent role for RV dysfunction in adverse outcomes in patients with HFpEF. Independent prognostic value of RV areas, but not TAPSE, was also observed in the Northwestern HFpEF Registry and may reflect the limited accuracy of 2-dimensional imaging in quantifying function of the structurally complex right ventricle. Indeed, recent data have demonstrated prognostically relevant impairments in RV function by 3-dimensional echocardiography-based RV ejection fraction not captured by RV FAC or tricuspid annular velocity (39).

The prevalence of significant aortic stenosis in the PARAGON-HF echocardiography study was low, with moderate or greater stenosis detected in only 2% of participants. Despite this, higher peak aortic valve velocity was a robust independent predictor of all studied endpoints. Peak aortic valve velocity is an established correlate of several CV (and HF) risk factors (40), and residual confounding is a possible explanation. Stenosis severity was based solely on peak velocity, which may underestimate severity in the setting of reduced stroke volume. However, the generally normal LV chamber size and low prevalence of concentric hypertrophy do not suggest a classical remodeling pattern associated with low-flow aortic stenosis with preserved LVEF. Despite this, our findings support the need for future studies more fully characterizing aortic valve function in HFpEF.

Unexpectedly, LA size was not prognostic in PARAGON-HF. LA volume has been shown to be a reliable estimator of chronic LV filling pressure and to predict incident HF in the community and adverse outcomes in HFpEF and HF with reduced ejection fraction (19,41). Indeed, LA size was prognostic of outcomes in both the TOPCAT and I-PRESERVE echocardiography substudies (9,10). However, to qualify for enrollment in PARAGON-HF, all patients needed to have either LA enlargement or LV wall thickness ≥1.1 cm, and LA enlargement was present in the large majority of patients. It is therefore likely that the selection of patients with LA enlargement limited its predictive value in this study population.

STUDY LIMITATIONS. Although centrally analyzed, a portion of the echocardiograms included in this analysis were clinical echocardiograms and could have been performed within 6 months of screening. Because of this, certain echocardiographic views or measures, particularly Doppler measures, were missing in a subset of patients. However, similar findings were observed in sensitivity analyses using multiple imputation for missing echocardiographic data. In addition, although the study protocol

precluded intercurrent myocardial infarction, we cannot exclude that cardiac structure and function may have changed for other reasons during this period. Compared with PARAGON-HF participants not included in the echocardiography study, minor differences were observed in baseline characteristics compared with those included, potentially limiting the generalizability of these findings. However, supplemental analyses using inverse probability weights demonstrated similar results. Mineralocorticoid receptor antagonists have been associated with improved clinical outcomes and improvement in echocardiographic measures in HFpEF (25,42,43) and were being used in 23% of patients at baseline. We adjusted for their use in multivariate models relating echocardiographic measures to clinical outcomes. Finally, clinical trials by necessity impose inclusion and exclusion criteria, and therefore these findings may not be generalizable to community-based cohorts.

CONCLUSIONS

Echocardiographic findings from the 1,097 participants enrolled in PARAGON-HF demonstrate a high prevalence of LA enlargement, elevated filling pressure, pulmonary hypertension, and RV dysfunction. Higher LVMi, E/e′ ratio, PASP, and RV size were each associated with heightened risk for HF hospitalization or CV death independent of clinical comorbidities and NT-proBNP. Differences in LV and LA structure among patients enrolled in PARAGON-HF, TOPCAT, and I-PRESERVE, despite similarly elevated E/e′ ratios and clinical event rates, highlight the phenotypic and pathophysiologic heterogeneity of the HFpEF syndrome.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients with HFpEF enrolled in the PARAGON-HF trial, there was considerable variability of Doppler echocardiographic characteristics. Those with greater LV mass, measures of LV and RV filling pressure, and RV enlargement faced a relatively high risk for hospitalization for HF and CV death.

TRANSLATIONAL OUTLOOK: Future investigations should explore the extent to which echocardiographic measures of cardiac structure and function identify physiologically relevant subgroups that respond differentially to treatment.

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