Circulation: Heart Failure

ORIGINAL ARTICLE

Relationship Between Cardiac Structure and Function With Renal Function Trajectory and Outcomes in Patients With Heart Failure: Insights From the PARAGON-HF Trial

Henri Lu, MD; Safia Chatur, MD; Sahmin Lee, MD, PhD; Riccardo M. Inciardi, MD, PhD; Martin Abanda, MD; Finnian R. Mc Causland, MBBCh, MMSc; Arzu Kalayci, MD, MMSc; Kimia Karimi Taheri, MD; Amil M. Shah, MD, MPH; Maja Cikes, MD, PhD; Brian L. Claggett, PhD; Narayana Prasad, MD, MPH; Carolyn S.P. Lam, MBBS, PhD; Eileen O'Meara, MD; Xiaowen Wang, MD, MPH; John J.V. McMurray, MD; Marc A. Pfeffer, MD, PhD; Sheila M. Hegde, MD, MPH; Scott D. Solomon, MD; Hicham Skali, MD, MSc

BACKGROUND: Renal dysfunction is common and associated with a poor prognosis in patients with heart failure. However, the association of cardiac structure and function with decline in kidney function in this population is unknown. We aimed to assess the association between individual measures of cardiac structure and function with changes in renal function and renal outcomes in patients with heart failure with preserved ejection fraction.

METHODS: Patients enrolled in the PARAGON-HF (Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor With Angiotensin-Receptor Blockers Global Outcomes in Heart Failure With Preserved Ejection Fraction) echocardiographic substudy were included. The association between each echocardiographic parameter (expressed in standardized units) and changes over time in estimated glomerular filtration rate was calculated with repeated-measures mixed-effect models. Multivariable Cox proportional hazards models were used to identify individual cardiac parameters associated with the composite renal outcome (≥50% decline in estimated glomerular filtration rate relative to baseline, development of end-stage renal disease, or death attributable to renal causes), after adjusting for covariates.

RESULTS: Among 1097 patients (mean age 74±8 years and 53% women), over a median follow-up of 2.9 years, 28 composite renal events (0.9 per 100 person-years) occurred. Higher left ventricular (LV) mass index and higher E/average e′ ratio were associated with significantly more profound annual decline in estimated glomerular filtration rate (for both, −0.4 [95% CI, −0.7 to −0.1] mL/min/1.73 m^2/y per 1 higher SD). Higher LV mass index, LV end-diastolic volume index, right ventricular end-diastolic area, and a lower right ventricular fractional area change were each associated with a significantly higher risk for the composite renal outcome.

CONCLUSIONS: In the PARAGON-HF echocardiographic substudy, higher LV mass and filling pressures were independently associated with more profound kidney function decline, and higher LV mass and volume, as well as impaired right ventricular structure and function, were each associated with renal events. Assessing these parameters may help identify patients with heart failure with preserved ejection fraction at higher risk for adverse renal events and indicate potential therapeutic targets.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01920711.

Key Words: glomerular filtration rate ■ heart failure ■ kidney disease ■ kidney failure, chronic ■ prognosis

Correspondence to: Hicham Skali, MD, MSc, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis St, Boston, MA 02115. Email hskali@bwh.harvard.edu

This manuscript was sent to Kristina H. Haugaa, MD, PhD, Guest Editor, for review by expert referees, editorial decision, and final disposition.
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCHEARTFAILURE.124.011942.
For Sources of Funding and Disclosures, see page XXX.

Circulation: Heart Failure is available at www.ahajournals.org/journal/circheartfailure

WHAT IS NEW?

- Among patients with heart failure with preserved ejection fraction enrolled in the echocardiographic study of the PARAGON-HF trial (Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor With Angiotensin-Receptor Blockers Global Outcomes in Heart Failure With Preserved Ejection Fraction), higher left ventricular mass and higher left ventricular filling pressures were each independently associated with significant declines in kidney function over time.
- Additionally, higher left ventricular mass and volume, along with impaired right ventricular structure and function, were independently associated with a combined renal outcome that included a substantial decline (>50% relative to baseline) in estimated glomerular filtration rate, progression to end-stage renal disease, or death attributed to renal causes.

WHAT ARE THE CLINICAL IMPLICATIONS?

- In clinical practice, the assessment of these echocardiographic parameters may allow for more precise risk stratification in patients with heart failure with preserved ejection fraction, helping identify those at high risk for adverse renal events or kidney function deterioration.

Nonstandard Abbreviations and Acronyms

AFF	atrial fibrillation of flutter
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
eGFR	estimated glomerular filtration rate
FAC	fractional area change
HFpEF	heart failure with preserved ejection fraction
HR	hazard ratio
LA	left atrium
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVMi	left ventricular mass index
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PARAGON-HF	Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor With Angiotensin-Receptor Blockers Global Outcomes in HFpEF
RV	right ventricle
SBP	systolic blood pressure

Chronic kidney disease (CKD) is highly prevalent in heart failure with preserved ejection fraction (HFpEF), affecting up to 60% of patients.[1,2] While it is associated with a worse prognosis and higher risk of adverse clinical outcomes,[2,3] new treatments have recently demonstrated efficacy in slowing the decline of kidney function in patients with HFpEF.[4–6] The frequent coexistence of HFpEF and renal dysfunction can be partly attributed to shared risk factors and a bidirectional interplay between the heart and the kidneys with similarities in their pathophysiological mechanisms, as part of cardiorenal syndromes.[7,8]

Among patients with HF and those with CKD, previous studies have consistently shown an association between lower estimated glomerular filtration rate (eGFR) and abnormal cardiac structure and function assessed by echocardiography.[1,9–12] These abnormalities included left ventricular (LV) remodeling and hypertrophy (LVH), LV dilation, and impairment of both systolic and diastolic function. However, most studies were cross-sectional in design, and it remains uncertain whether alterations in cardiac structure and function may impact renal function, especially in patients with HF. Furthermore, many studies used conventional echocardiographic parameters to describe cardiac mechanics and did not include speckle-tracking, which has been shown to be superior in detecting subtle impairment of the LV,[13] right ventricle (RV),[14] and left atrium (LA).[15]

In this post hoc analysis of the PARAGON-HF trial (Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor With Angiotensin-Receptor Blockers Global Outcomes in Heart Failure With Preserved Ejection Fraction), utilizing data from the well-characterized echocardiographic substudy cohort, our main objectives were 3-fold: first, to cross-sectionally characterize the association between baseline eGFR and clinical and echocardiographic parameters; second, to investigate the association between individual impaired echocardiographic parameters (including LV and RV strain analyses) with the trajectory of kidney function; and third, to identify specific echocardiographic parameters that may be associated with clinical renal outcomes.

METHODS

The sponsor of the PARAGON-HF trial is committed to sharing access to patient-level data and supporting clinical documents from eligible studies with qualified external researchers. Requests for access undergo review by an independent review panel, considering scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

Patient Population

The designs of the PARAGON-HF trial and the echocardiographic substudy have been previously published.[16–18] In brief, PARAGON-HF was a multicenter, randomized, event-driven trial involving 4796 patients, who were randomized to receive either sacubitril/valsartan or valsartan after a sequential run-in period. Key inclusion criteria included age ≥50 years,

HF requiring diuretic treatment and with New York Heart Association functional class II to IV symptoms, a LV ejection fraction (LVEF) ≥45% on echocardiography with features of structural heart disease (LVH or LA enlargement), and elevated natriuretic peptide levels. Notable exclusion criteria comprised a history of LVEF <40%, isolated right HF, symptomatic hypotension (or a systolic blood pressure [SBP] <110 mm Hg at screening or <100 mm Hg at randomization), and impaired kidney function (an eGFR <30 mL/min/1.73 m^2 at screening). The trial was approved by an ethics committee or institutional review board at each participating site, and all patients provided written informed consent before enrollment.

The echocardiographic substudy was designed to better characterize the cardiac phenotype in the trial population and for quality control purposes.[18] Qualifying echocardiograms were analyzed at the echocardiography core laboratory of Brigham and Women's Hospital (Boston, MA) within 6 months of the screening visit. If unavailable, a screening echocardiographic exam was used with a study-specific imaging protocol. Consent for reviewing historical and screening echocardiograms was obtained on the main study consent form. A total of 1097 participants had sufficient image quality for LVEF quantification and available baseline eGFR data and were included in this analysis.

Echocardiography

Echocardiographic exams were sent in a digital format to the core laboratory, where quantitative analyses of 2-dimensional, Doppler, and tissue Doppler measurements were made. All measurements were performed in triplicate by the same analyst for all study participants, adhering to the guidelines set by the American Society of Echocardiography.[19] The analysts were blinded to clinical information and randomized treatment assignments. Intraobserver and interobserver variability for key cardiac structural and functional parameters have been previously published.[20]

LV volumes were calculated using the modified biplane Simpson's rule in the apical 4- and 2-chamber views, and LVEF was determined in the standard fashion from LV end-diastolic and LV end-systolic volumes.[19] When apical views were of poor quality or missing, the Teichholz method was used to determine LVEF (n=200).[21] LV mass was estimated using the ASE recommended formula and indexed to body surface area (LV mass index [LVMi]). LVH was considered to be present if LVMi was ≥115 g/m^2 in men and ≥95 g/m^2 in women.[19] 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). For diastolic function, mitral inflow velocity was assessed using pulsed-wave Doppler from the apical 4-chamber view, and peak early diastolic tissue velocity (e′) was measured at the septal and lateral sides of the mitral annulus. Conventional RV functional measures included tricuspid annular plane systolic excursion and RV fractional area change (FAC). Tricuspid annular plane systolic excursion was measured by assessing the systolic excursion of the tricuspid annulus, while RV FAC was determined from the cavity area at end-diastole and end-systole. Thresholds defining abnormality were based on the ASE guidelines: <1.7 cm for tricuspid annular plane systolic excursion and <35% for FAC.[19] Peak tricuspid regurgitation velocity was measured, and pulmonary artery systolic pressure was calculated using the following formula: 4×(peak tricuspid regurgitation velocity)^2+5. Speckle-tracking analysis was performed using the semi-automated software TOMTEC Imaging Systems (Image-Arena, version 4.6.6.3; Munich, Germany). This software tracks multiple chamber reference points over time to identify cardiac motion. Data for LV and LA longitudinal deformation were obtained from apical 4-chamber and 2-chamber views. RV free wall longitudinal strain was traced from the RV-focused apical 4-chamber view and calculated as the mean value of longitudinal strains from the basal, middle, and apical segments of the RV free wall during ventricular systole. We selected RV free wall longitudinal strain because it is not affected by ventricular interdependence.

Because of wall shortening during contraction, the LV global longitudinal strain and RV free wall longitudinal strain values are in theory negative, but for the purpose of our analysis, we reported positive (absolute) values. Absolute values <20% for both LV global longitudinal strain and RV free wall longitudinal strain were considered abnormal.[19,22] LA conduit strain and contraction strain were also reported as absolute values.

Definition of Renal Function and Outcomes

All eGFR values were calculated using the 2021 creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) without race equation.[23] This differed from previous papers of the PARAGON-HF trial, in which baseline eGFR was estimated according to the Modification of Diet in Renal Disease formula, and follow-up eGFR was calculated using a previous version of the CKD-EPI equation.[4,17] Creatinine levels were assessed using dilution mass spectrometry. Measurements were taken at randomization, weeks 4, 16, 32, and 48, then every 24 weeks until week 120, and thereafter, every 12 weeks until week 216, resulting in a total of 16 visits with a median interval of 12 weeks between visits. However, data from weeks 192 to 216 were excluded from our analyses due to missing values. For tabulation and classification purposes, the distribution of baseline eGFR was categorized into 4 groups (<45, ≥45 and <60, ≥60 and <75, and ≥75 mL/min/1.73 m^2). The cutoff values were chosen to ensure an equal balance of patients in each group, following a similar approach in previous reports.[10] Of note, patients with severely impaired kidney function (an eGFR of <30 mL/min/1.73 m^2 at screening or <25 mL/min/1.73 m^2 at randomization, using the Modification of Diet in Renal Disease formula) were excluded from the PARAGON-HF trial.

The change in kidney function over time relative to baseline was assessed for each baseline echocardiographic parameter, specifically examining the change associated with a 1 SD increase in each parameter. The composite renal outcome, a prespecified secondary outcome, was defined as either: a ≥50% decline in eGFR relative to baseline, development of end-stage renal disease, or death attributable to renal causes. Renal end point definitions have been previously published.[4]

Statistical Analyses

Continuous variables were presented as means±SD or as medians with 25th to 75th percentiles. To examine trends

across groups for binary variables, the Cochran-Armitage test was used. Linear regression was applied for normally distributed continuous variables, while Cuzick's nonparametric test was used for non-normally distributed variables. Adjusted baseline echocardiographic parameters according to eGFR groups were calculated using linear regression models and adjusting for age, sex, body mass index, race, enrollment region, hypertension, diabetes, any history of atrial fibrillation of flutter (AFF), and randomized treatment arm (sacubitril/valsartan or valsartan).

To analyze the annual decline in eGFR, repeated-measures mixed-effect models were used. After adjusting for age, sex, race, body mass index, SBP, AFF, diabetes, ischemic cause, randomized treatment arm (sacubitril/valsartan or valsartan), and baseline eGFR, we examined the relationship between each standardized echocardiographic parameter at baseline and the change in annual decline of eGFR, using mixed-effects models for repeated measurements. Additionally, we modeled the change in eGFR over time for echocardiographic parameters found to be significant, categorizing each parameter based on its median values.

Finally, multivariable Cox proportional hazard models were used to identify individual cardiac structural and functional parameters associated with the composite renal outcome, adjusting each echocardiographic parameter for age, SBP, diabetes, treatment arm, and baseline eGFR. Each parameter was categorized based on medians, with the lower median group used as the reference category. We further examined the continuous association between echocardiographic parameters identified as significant in the previous step and the composite renal outcome using restricted cubic splines, with the numbers of knots selected to minimize the resulting Akaike Information Criteria (3–6 knots tested). All *P* values were 2-sided; a $P<0.05$ was used to denote statistical significance. Statistical analyses were performed using the Stata software, version 18.0 (Stata Corp, College Station, TX).

RESULTS

Study Population

A comparison between PARAGON-HF patients enrolled in the echocardiography cohort with available baseline eGFR (n=1097, mean age 74±8 years, 53% women) and the remainder (n=3699) has been previously published.[18] The baseline mean eGFR of patients in the echocardiographic substudy, calculated using the 2021 CKD-EPI formula, was 64.1±19.2 mL/min/1.73 m². This value was slightly but statistically significantly lower than the mean eGFR of patients not included in the echocardiographic substudy, which was 67.3±18.4 mL/min/1.73 m² ($P<0.001$). Baseline eGFR using the 2021 CKD-EPI formula was also higher than previously reported in patients enrolled in the echocardiographic substudy (60.5±18.3 mL/min/1.73 m^2), which was based on the Modification of Diet in Renal Disease formula.[18]

Baseline Kidney Function

Among patients enrolled in the echocardiographic cohort, 583 (53%) had an eGFR <60 mL/min/1.73 m^2. Reduced eGFR at baseline was associated with older age, female sex, different enrollment regions (more patients from North America and Western Europe), a higher New York Heart Association functional class, a higher prevalence of AFF, hypertension, stroke and chronic obstructive pulmonary disease, and higher NT-proBNP (N-terminal pro-B-type natriuretic peptide) values, as well as lower systolic and diastolic BP (Table 1). Finally, patients in the lower eGFR categories were less likely to be prescribed angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or oral anticoagulation therapy.

Unadjusted echocardiographic data are presented in Table 2. Patients in the higher categories of eGFR had smaller LV cavity dimensions, higher LVEF, higher indices of LV filling pressures, and greater impairment in LA contractile strain. There was no significant change in RV structure and function by eGFR category. After adjusting for age, sex, body mass index, race, enrollment region, hypertension, diabetes, history of AFF, and randomized treatment arm, none of the previously mentioned associations remained significant (Table 3).

Kidney Function Trajectory

On longitudinal follow-up, the mean decline of eGFR was −2.5 (95% CI, −2.8 to −2.2) mL/min/1.73 m^2 per year. After multivariable adjustment for covariates (age, sex, race, body mass index, SBP, AFF, diabetes, ischemic cause, treatment arm, baseline eGFR), higher LVMi and higher E/average e′ ratio were each independently and significantly associated with more pronounced annual decline in eGFR (Table 4). A similar association was found for tricuspid regurgitation velocity (only available in 483 patients), which, however, did not reach statistical significance ($P=0.08$). The mean change in eGFR from randomization during follow-up according to LVMi medians and E/average e′ medians is shown in Figure 1.

Composite Renal Outcome

After a median follow-up period of 2.9 years, there were 28 composite renal events (0.9 events per 100 patient-years), mainly driven by the individual component of ≥50% reduction in eGFR from baseline, which occurred in 27 patients (the remaining patient had end-stage renal disease). After adjusting for age, baseline eGFR, SBP, and treatment arm, higher LV end-diastolic volume index (adjusted hazard ratio [HR], 3.41 [95% CI, 1.23–10.44]), LV posterior wall thickness (adjusted HR, 2.64 [95% CI, 1.06–6.62]), and LVMi (adjusted HR, 3.31 [95% CI, 1.24–8.86]) were each significantly associated with a higher risk for the composite renal outcome

Table 1. Baseline Clinical Characteristics According to Baseline eGFR Category

	<44 mL/min·m² (n=182)	45–59 mL/min·m² (n=317)	60–74 mL/min·m² (n=281)	≥75 mL/min·m² (n=317)	P_{trend}
Age, y	76.1±7.8	76.4±7.4	73.8±7.2	69.6±7.7	<0.001
Female sex	113 (62.1)	163 (51.4)	160 (56.9)	143 (45.1)	0.002
BMI, kg/m²	30.7±4.8	29.6±5.0	29.7±5.0	29.9±4.8	0.31
Race					0.67
Asian	29 (15.9)	38 (12.0)	40 (14.2)	52 (16.4)	
Black	10 (5.5)	13 (4.1)	13 (4.6)	5 (1.6)	
White	141 (77.5)	265 (83.6)	226 (80.4)	255 (80.4)	
Native American	0 (0.0)	1 (0.3)	1 (0.4)	1 (0.3)	
Other	2 (1.1)	0 (0.0)	1 (0.4)	4 (1.3)	
Enrollment region					<0.001
Asia/Pacific and other	30 (16.5)	45 (14.2)	50 (17.8)	58 (18.3)	
Central Europe	20 (11.0)	52 (16.4)	67 (23.8)	104 (32.8)	
Latin America	3 (1.6)	2 (0.6)	6 (2.1)	4 (1.3)	
North America	70 (38.5)	112 (35.3)	74 (26.3)	68 (21.5)	
Western Europe	59 (32.4)	106 (33.4)	84 (29.9)	83 (26.2)	
NYHA classification					0.003
I	7 (3.8)	12 (3.8)	10 (3.6)	12 (3.8)	
II	123 (67.6)	237 (74.8)	219 (77.9)	254 (80.1)	
III	50 (27.5)	68 (21.5)	52 (18.5)	51 (16.1)	
IV	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	
SBP, mm Hg	126±15	128±17	129±16	131±16	<0.001
DBP, mm Hg	69±11	70±11	73±11	75±11	<0.001
Heart rate, beats/min	69±13	69±13	70±13	70±12	0.46
eGFR, mL/min·m²	38.5±4.7	52.9±4.3	67.3±4.3	87.4±8.4	By design
Prior MI	37 (20.3)	75 (23.7)	46 (16.4)	75 (23.7)	0.82
Ischemic cause	53 (29.1)	107 (33.8)	74 (26.3)	99 (31.2)	0.83
AFF at screening	65 (35.9)	114 (36.1)	106 (38.0)	95 (30.1)	0.17
Any AFF*	123 (67.6)	210 (66.2)	179 (63.7)	157 (49.5)	<0.001
Prior HFH	93 (51.1)	142 (44.8)	120 (42.7)	151 (47.6)	0.60
Hypertension	178 (97.8)	301 (95.0)	258 (91.8)	293 (92.4)	0.008
Diabetes	82 (45.1)	126 (39.7)	100 (35.6)	133 (42.0)	0.54
Prior stroke	26 (14.4)	41 (13.1)	29 (10.3)	30 (9.5)	0.05
COPD	34 (18.7)	57 (18.0)	35 (12.5)	36 (11.4)	0.005
Diuretics	176 (96.7)	305 (96.2)	275 (97.9)	291 (91.8)	0.011
MRA	44 (24.2)	68 (21.5)	74 (26.3)	69 (21.8)	0.87
ACE inhibitor/ARB	135 (74.2)	258 (81.4)	234 (83.3)	267 (84.2)	0.009
BB	154 (84.6)	231 (72.9)	229 (81.5)	254 (80.1)	0.83
Digoxin	12 (6.6)	29 (9.1)	31 (11.0)	32 (10.1)	0.19
Statin	126 (69.2)	201 (63.4)	179 (63.7)	216 (68.1)	0.88
Antiplatelet	29 (15.9)	37 (11.7)	30 (10.7)	47 (14.8)	0.96
OAC	102 (56.0)	175 (55.2)	163 (58.0)	144 (45.4)	0.019
Pacemaker	22 (12.1)	39 (12.3)	36 (12.8)	29 (9.1)	0.28
ICD	2 (1.1)	3 (0.9)	1 (0.4)	1 (0.3)	0.19
Randomized to sac/val	95 (52.2)	165 (52.1)	140 (49.8)	161 (50.8)	0.66
NT-proBNP, pg/mL	1217 (580, 2077)	1020 (594, 1699)	918 (494, 1572)	698 (390, 1216)	<0.001
KCCQ					
Clinical summary score	73 (57, 86)	75 (57, 88)	77 (59, 92)	76 (55, 85)	0.95
Overall summary score	75 (58, 83)	74 (56, 85)	74 (58, 90)	74 (55, 85)	0.94

ACE indicates angiotensin-converting enzyme; AFF, atrial fibrillation and flutter; ARB, angiotensin receptor blocker; BB, beta-blockers; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HFH, heart failure hospitalization; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OAC, oral anticoagulation; sac/val, sacubitril/valsartan; and SBP, systolic blood pressure.

*History of AFF or AFF at screening.

Values are expressed as n (%), mean±SD, or median (25th, 75th percentiles).

Table 2. Unadjusted Baseline Echocardiographic Characteristics According to Baseline eGFR Category

	<44 mL/min·m² (n=182)	45–59 mL/min·m² (n=317)	60–74 mL/min·m² (n=281)	≥75 mL/min·m² (n=317)	P_{trend}
LV structure					
LVEDVi, mL/m²	49.9±16.1	51.5±15.9	52.0±16.4	56.5±18.0	<0.001
LVESVi, mL/m²	20.7±9.8	21.1±9.5	21.7±10.7	24.9±11.7	<0.001
LV mean wall thickness, cm	1.02±0.20	1.04±0.21	1.03±0.20	1.02±0.19	0.06
LV mass index, g/m²	86.3±27.0	86.9±24.8	86.4±27.9	89.2±26.8	0.048
LV RWT	0.43±0.13	0.44±0.13	0.43±0.12	0.41±0.11	<0.001
LV hypertrophy	49 (26.9%)	82 (25.9%)	75 (26.7%)	90 (28.4%)	0.60
LV function					
LVEF, %	58.7±7.2	59.2±7.8	58.6±7.5	57.7±7.9	0.041
Abs. LV GLS, %	15.9±3.7	16.4±3.6	15.9±3.4	16.0±3.7	0.55
Mitral E wave, cm/s	95.0±29.0	90.3±27.8	89.9±28.7	86.9±25.9	0.006
E/A ratio	1.3±0.8	1.4±0.7	1.4±0.8	1.2±0.6	0.26
Septal e′, cm/s	5.7±1.8	5.6±1.7	5.8±1.8	6.0±1.9	0.032
Lateral e′, cm/s	7.9±2.4	7.7±2.3	7.8±2.5	8.2±2.8	0.13
E/average e′	15.8±6.1	15.2±6.6	14.7±6.7	13.8±5.9	0.002
LA structure and function					
LA volume, mL	72.7±27.4	73.7±26.4	78.2±37.8	73.8±25.0	0.50
LA volume index, mL/m²	37.9±13.2	38.5±13.7	40.9±20.2	37.9±13.2	0.80
LA reservoir strain, %	15.7±9.5	15.9±10.4	15.0±10.4	17.5±11.3	0.11
Abs. LA conduit strain, %	10.0±5.6	10.6±6.3	10.3±6.3	11.1±6.9	0.13
Abs. LA contractile strain, %	6.8±5.5	7.2±6.4	6.9±6.1	8.4±7.0	0.017
RV structure and function					
RV EDA, cm²	21.6±6.9	20.4±5.5	21.2±5.4	21.2±6.2	0.97
RV ESA, cm²	11.6±4.9	10.9±3.6	11.2±3.7	11.3±4.4	0.80
RV FAC, %	47.0±10.0	46.5±9.4	47.5±8.7	47.2±9.2	0.57
TAPSE, cm	1.80±0.43	1.76±0.43	1.82±0.44	1.85±0.38	0.16
Abs. RV FWLS, %	17.9±6.0	19.3±6.8	18.7±6.7	19.7±7.6	0.13
TR velocity, m/s	2.70±0.52	2.70±0.50	2.63±0.37	2.63±0.46	0.16
PASP, mm Hg	35.3±11.7	35.2±11.5	33.3±8.0	33.6±10.8	0.11
TAPSE/PASP, mm/mm Hg	0.57±0.23	0.55±0.19	0.56±0.19	0.58±0.21	0.81
Abs. RVFWLS/PASP, %/mm Hg	0.56±0.26	0.60±0.26	0.58±0.22	0.62±0.26	0.36

Abs. indicates absolute; EDA, end-diastolic area; eGFR, estimated glomerular filtration rate; ESA, end-systolic area; FAC, fractional area change; GLS, global longitudinal strain; LA, left atrium; LV, left ventricle; LVEDVi, LV end-diastolic volume index; LVEF, LV ejection fraction; LVESVi, LV end-systolic volume index; PASP, pulmonary artery systolic pressure; RV, right ventricle; RVFWLS, RV free wall longitudinal strain; RWT, relative wall thickness; TAPSE, tricuspid annular plane systolic excursion; and TR, tricuspid regurgitation.

(Table 5). Higher RV end-diastolic area (adjusted HR, 4.68 [95% CI, 1.35–16.23]) and lower FAC (adjusted HR, 0.31 [95% CI, 0.11–0.88]) were also each associated with a higher risk of the composite renal outcome. Figure 2 illustrates the association between the adjusted incidence rate of the composite renal outcome and continuous LV end-diastolic volume index, LVMi, RV end-diastolic area, and FAC.

DISCUSSION

In this large and well-characterized cohort of patients with HFpEF who underwent echocardiography and had available longitudinal renal follow-up data, we found that (1) there was a lack of significant association between baseline eGFR and adjusted echocardiographic parameters of cardiac structure and function; (2) baseline higher LV mass and indices of high LV filling pressures were associated with a more profound decline in kidney function over time; (3) higher LV mass, altered LV structure, and impairment of RV structure and function at baseline were associated with a higher risk of renal events.

Prior studies have demonstrated that patients with renal impairment tend to have smaller, more hypertrophied LVs with greater levels of diastolic dysfunction.[9–12] In contrast, we found that all associations between echocardiographic parameters and baseline

Table 3. Adjusted Baseline Echocardiographic Characteristics According to Baseline eGFR Category

	<44 mL/min·m² (n=182)	45–59 mL/min·m² (n=317)	60–74 mL/min·m² (n=281)	≥75 mL/min·m² (n=317)	P_{trend}
LV structure					
LVEDVi, mL/m²	52.6	53.3	52.4	52.6	0.84
LVESVi, mL/m²	22.3	22.0	21.8	22.8	0.62
LV mean wall thickness, cm	1.01	1.03	1.03	1.03	0.33
LV mass index, g/m²	86.3	86.5	87.1	89.0	0.26
LV RWT	0.42	0.43	0.43	0.42	0.89
LV hypertrophy	25.3%	26.1%	26.8%	29.0%	0.38
LV function					
LVEF, %	58.0	59.1	58.6	58.2	0.78
Abs. LV GLS, %	15.8	16.3	15.8	16.2	0.81
Mitral E wave, cm/s	91.3	88.6	90.3	90.6	0.93
E/A ratio	1.3	1.3	1.4	1.3	0.87
Septal e′, cm/s	5.8	5.7	5.8	6.0	0.26
Lateral e′, cm/s	8.0	7.7	7.8	8.1	0.57
E/average e′	15.1	14.8	14.8	14.6	0.52
LA structure and function					
LA volume, mL	71.6	72.9	78.4	74.9	0.1
LA volume index, mL/m²	37.2	38.0	40.7	39.0	0.11
LA reservoir strain, %	16.7	16.6	15.3	15.8	0.18
Abs. LA conduit strain, %	10.6	10.9	10.3	10.4	0.49
Abs. LA contractile strain, %	7.4	7.6	7.1	7.5	0.99
RV structure and function					
RV EDA, cm²	21.6	20.6	21.3	20.9	0.67
RV ESA, cm²	11.5	11.0	11.2	11.2	0.87
RV FAC, %	47.3	46.7	47.5	46.8	0.91
TAPSE, cm	1.82	1.79	1.83	1.80	0.99
Abs. RV FWLS, %	18.8	19.7	18.4	18.7	0.54
TR velocity, m/s	2.65	2.69	2.64	2.68	0.96
PASP, mm Hg	34.3	35.0	33.4	34.6	0.78
TAPSE/PASP, mm/mm Hg	0.59	0.57	0.55	0.55	0.24
Abs. RVFWLS/PASP, %/mm Hg	0.58	0.61	0.57	0.59	0.9

Adjusted for age, sex, body mass index, race, enrollment region, hypertension, diabetes, any AFF, and treatment arm. Abs. indicates absolute; EDA, end-diastolic area; eGFR, estimated glomerular filtration rate; ESA, end-systolic area; FAC, fractional area change; GLS, global longitudinal strain; LA, left atrium; LV, left ventricle; LVEDD, LV end-diastolic diameter; LVEDVi, LV end-diastolic volume index; LVEF, LV ejection fraction; LVESD, LV end-systolic diameter; LVESVi, LV end-systolic volume index; PASP, pulmonary artery systolic pressure; PW, posterior wall; RV, right ventricle; RVFWLS, RV free wall longitudinal strain; RWT, relative wall thickness; TAPSE, tricuspid annular plane systolic excursion; and TR, tricuspid regurgitation.

eGFR lost significance after thorough adjustment for baseline clinical confounders, suggesting that the associations observed in previous analyses may have been influenced by patients' individual characteristics and comorbidities, affecting cardiac structure and function, rather than being solely attributed to renal dysfunction itself.

In longitudinal analyses, the mean annual decline of eGFR (−2.5 mL/min/1.73 m²) measured in the echocardiographic substudy was consistent with the decline observed in the main PARAGON-HF study[4] and lies in the same range as the eGFR slopes previously reported in other HFpEF populations.[24] LVMi emerged as an independent and robust predictor of both a worse trajectory in eGFR and adverse renal outcomes. Prior studies have shown a higher prevalence of LVH in patients with CKD, particularly in those with end-stage renal disease. However, the relationship between LVH and CKD is bidirectional, and limited research has focused on the impact of LVH on renal function, particularly in patients with HF. From a pathophysiological perspective, several explanations could

Table 4. Annual eGFR Change Associated with a 1 SD Increase for Each Echocardiographic Parameter

	No. of patients	Annual eGFR change, mL/min/1.73 m²/y	*P* value
LV structure			
LVEDVi, per 16.8 mL/m²	889	0 (−0.4 to 0.3)	0.82
LVESVi, per 10.6 mL/m²	889	−0.1 (−0.5 to 0.2)	0.48
LV mean wall thickness, per 2 mm	1006	−0.2 (−0.5 to 0.1)	0.20
LV mass index, per 26 g/m²	1005	−0.4 (−0.7 to −0.1)	0.005
LV RWT, per 0.12	1008	0 (−0.3 to 0.3)	0.83
LV function			
LVEF, per 7.7%	1086	0 (−0.3 to 0.3)	0.94
Absolute LV GLS, per 3.6%	783	0.1 (−0.3 to 0.4)	0.7
E/average e′, per 6.0	826	−0.4 (−0.7 to −0.1)	0.014
LA structure			
LA volume index, per 15.5 mL/m²	968	0 (−0.3 to 0.3)	0.92
LA reservoir strain, per 10.5%	922	0 (−0.3 to 0.4)	0.87
Absolute LA conduit strain, per 6.4%	874	0.1 (−0.2 to 0.4)	0.56
Absolute LA contractile strain, per 7.6%	874	0 (−0.4 to 0.3)	0.83
RV structure and function			
RV EDA, per 5.9 cm²	616	−0.2 (−0.6 to 0.2)	0.29
RV FAC, per 9.3%	616	0.1 (−0.2 to 0.5)	0.46
TAPSE, per 0.4 cm	509	0 (−0.4 to 0.4)	0.88
Absolute RVFWLS, per 6.8%	524	0.3 (−0.1 to 0.7)	0.13
TR velocity, per 0.5 m/s	483	−0.4 (−0.8 to 0)	0.08
PASP, per 10.5 mm Hg	483	−0.3 (−0.7 to 0.1)	0.10
TAPSE/PASP, per 0.2 mm/mm Hg	275	0.2 (−0.3 to 0.7)	0.36
RV FAC/PASP, per 0.5 cm²/mm Hg	311	0.4 (−0.1 to 0.8)	0.12
Absolute RVFWLS/PASP, per 0.24%/mm Hg	279	0.5 (0.1 to 1.0)	0.017

Each echocardiographic parameter is expressed per 1 SD. All analyses are adjusted for age, sex, race, body mass index, systolic blood pressure, any history of AFF, diabetes, ischemic cause, treatment arm (sacubitril/valsartan or valsartan), and baseline eGFR. AFF indicates atrial fibrillation or flutter; EDA, end-diastolic area; eGFR, estimated glomerular filtration rate; FAC, fractional area change; GLS, global longitudinal strain; LA, left atrium; LV, left ventricle; LVEDVi, LV end-diastolic volume index; LVEF, LV ejection fraction; LVESVi, LV end-systolic volume index; PASP, pulmonary artery systolic pressure; PW, posterior wall; RV, right ventricle; RVFWLS, RV free wall longitudinal strain; RWT, relative wall thickness; TAPSE, tricuspid annular plane systolic excursion; and TR, tricuspid regurgitation.

account for this association in patients with HFpEF. Hypertension, a primary contributor to LVH, can result in gradual kidney alterations characterized by pathological changes such as arteriosclerosis, cortical fibrosis, tubular atrophy and loss, and glomerulosclerosis that are pathologically referred to as hypertensive angiosclerosis.[25] Additionally, the development of LVH and CKD in HFpEF may share common etiologies (eg, anemia) or pathophysiological pathways, including neurohumoral activation, increased mechanical load, endothelial dysfunction, and a low-grade systemic inflammatory state mediated by hypertension, obesity, and diabetes.[26] From a clinical perspective, the role of LVH as a prognostic marker is not novel, as previous studies have correlated it with a higher risk of hospitalization for HF or cardiovascular death in patients with HFpEF.[18] Our study provides new data by demonstrating that this association also extends to kidney-related events, and notably, this association is evident despite a relatively small number of events in our study.

An interesting difference between the predictors of kidney function trajectory and renal events lies in the observation that indices reflecting high LV filling pressures (such as the E/e′ ratio) were found to predict the former but not the latter, whereas RV size and function were predictive of the composite renal outcome alone. This difference may stem from differences in the definition of outcomes and their associated severity, as renal events may indicate a more advanced stage of kidney disease. RV dysfunction is partly attributed to the chronic volume overload and backward transmission of elevated LV filling pressures and widely acknowledged as a prognostic factor in HFpEF patients.[27] Our findings underscore the crucial role of elevated renal venous pressure resulting from RV dysfunction in the development of HF-related renal disease.[28] Elevated renal venous pressure increases hydrostatic pressures in the interstitial and tubular regions of the kidneys and decreases renal perfusion pressure and the flow of blood to the kidneys, all of which contribute to a reduction in GFR.[29] Furthermore, the heightened venous pressure can trigger hypoxia and activate local and systemic neurohormonal responses, which further compromise kidney function in these patients.[30] In contrast, higher E/e′ ratio was only predictive of a decline in kidney function, suggesting that the elevation of LV filling pressure may be associated with a more gradual and continuous deterioration of renal function over time. The differences observed in the identified predictors of kidney function trajectory and renal events may arise due to the divergent nature of these outcomes and the fact that they assess different stages of kidney disease. The first outcome reflects a continuous change over time with repeated eGFR measurements, whereas the second one uses a dichotomous variable to denote an event, possibly indicative of a more advanced stage of kidney disease.

Incorporating the echocardiographic measures we identified into clinical practice may allow for more precise risk stratification in patients with HFpEF, helping

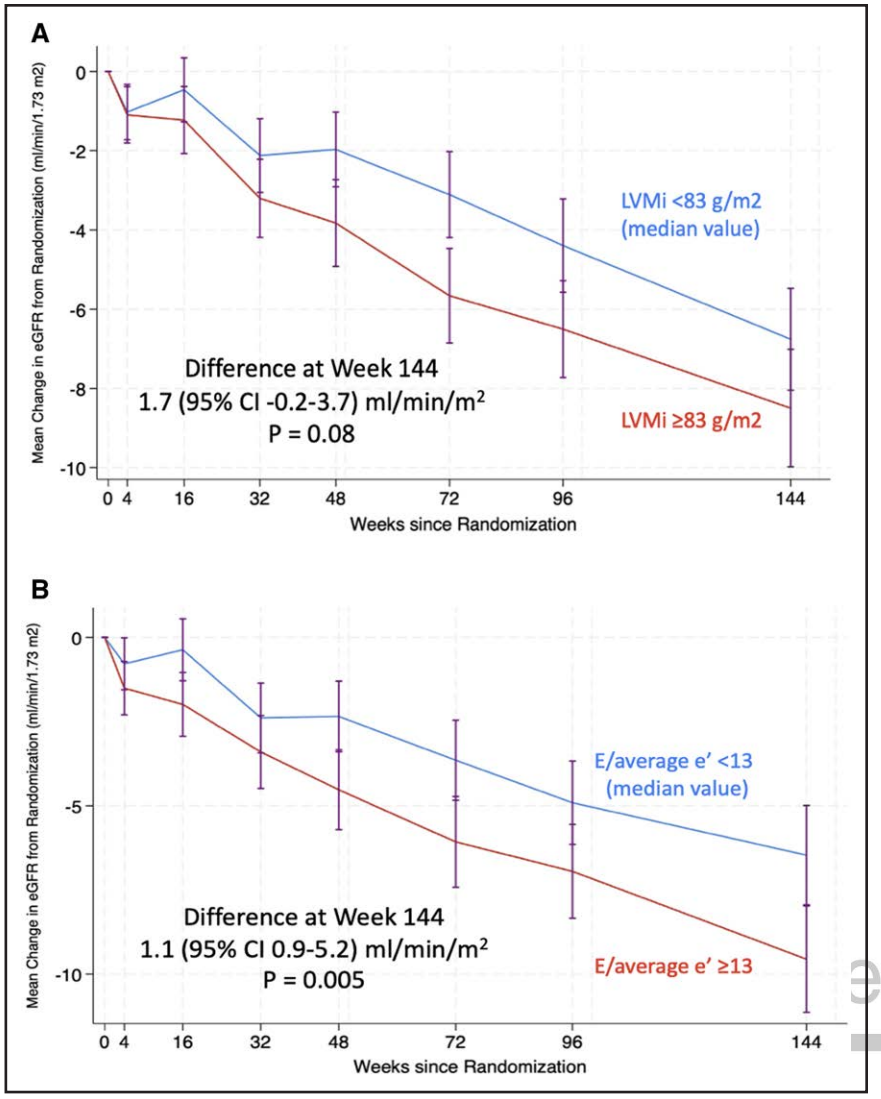

Figure 1. Mean change in eGFR from baseline during follow-up according to LVMi median and E/ e′ median. **A**, LVMi median; **B**, E/average e′ median. All echocardiographic parameters were measured at baseline. eGFR indicates estimated glomerular filtration rate; and LVMi, left ventricular mass index.

to identify those at higher risk of adverse renal events. However, it remains unclear whether these measures can serve as potential therapeutic targets.

Limitations

Several limitations need to be acknowledged. First, this is a post hoc analysis of a randomized clinical trial, and therefore results should be considered hypothesis-generating. Furthermore, our results may not be generalizable to all HFpEF populations in the community, given the inclusion and exclusion criteria of the PARAGON-HF trial and the differences between patients enrolled in the echocardiographic substudy and the remaining ones regarding baseline kidney function. Second, data on right atrial structure and function, as well as the severity of valvular regurgitation (particularly tricuspid), were not collected. This information could have provided additional insights into the pathophysiology of elevated venous pressure and its impact on renal function. Third, while the concomitant use of cystatin C and creatinine for precise GFR estimation is recommended,[31] we only had access to creatinine data in our study. To partially address this limitation, we utilized the most recent version of the CKD-EPI formula. Additionally, spot urine samples were not available, and parameters such as urinary albumin and creatinine concentrations, which have been used in other studies, were not present in our study. Fourth, echocardiography was performed only at baseline, precluding examination of changes in echocardiographic parameters with change in renal function over time, and not all echocardiographic parameters were universally available for all patients, potentially affecting the robustness of certain results. Finally, the course of kidney disease may also be altered by an increased use of sodium-glucose cotransporter-2 inhibitors (not yet in use in the PARAGON-HF trial) and mineralocorticoid

Table 5. Key Echocardiographic Predictors of the Composite Renal Outcome

	Available in n patients	Events, n (%)	Event rate (95% CI)	Unadjusted HR	Adjusted HR*
LVEDVi	897				
≥50.3 mL/m² (median value)		19 (4.2)	1.4 (0.9–2.3)	3.91 (1.46–10.49)	3.41 (1.23–10.44)
<50.3 mL/m²		5 (1.1)	0.4 (0.2–0.9)	1 (reference)	1 (reference)
LV posterior wall	1021				
≥0.9 cm (median value)		20 (3.9)	1.3 (0.8–2.0)	2.99 (1.20–7.46)	2.64 (1.06–6.62)
<0.9 cm		6 (1.2)	0.4 (0.2–0.9)	1 (reference)	1 (reference)
LV mass index	1015				
≥82.9 g/m² (median value)		21 (4.1)	1.4 (0.9–2.1)	4.10 (1.55–10.88)	3.31 (1.24–8.86)
<82.9 g/m²		5 (1.0)	0.3 (0.1–0.8)	1 (reference)	1 (reference)
LVEF	1097				
≥59.0% (median value)		11 (2.0)	0.7 (0.4–1.2)	0.63 (0.30–1.35)	0.71 (0.33–1.53)
<59.0%		17 (3.1)	1.1 (0.7–1.7)	1 (reference)	1 (reference)
Absolute LV GLS	790				
≥16.4% (median value)		8 (2.0)	0.7 (0.3–1.4)	0.64 (0.26–1.56)	0.59 (0.24–1.49)
<16.4%		12 (3.0)	1.0 (0.6–1.8)	1 (reference)	1 (reference)
E/average e′	833				
≥13.4 (median value)		11 (2.6)	0.9 (0.5–1.7)	1.17 (0.50–2.75)	0.97 (0.40–2.35)
<13.4		10 (2.4)	0.8 (0.4–1.5)	1 (reference)	1 (reference)
LA volume index	978				
≥37.2 mL/m² (median value)		15 (3.1)	1.1 (0.6–1.8)	1.23 (0.59–2.60)	1.43 (0.67–3.04)
<37.2 mL/m²		13 (2.7)	0.9 (0.5–1.5)	1 (reference)	1 (reference)
RV EDA	620				
≥20.0 cm² (median value)		15 (4.8)	1.6 (1.0–2.7)	4.98 (1.44–17.21)	4.68 (1.35–16.23)
<20.0 cm²		3 (1.0)	0.3 (0.1–1.0)	1 (reference)	1 (reference)
RV FAC	620				
≥47.0% (median value)		5 (1.6)	0.5 (0.6–1.5)	0.31 (0.11–0.88)	0.31 (0.11–0.88)
<47.0%		13 (4.2)	1.5 (0.9–2.7)	1 (reference)	1 (reference)
TAPSE	515				
≥1.76 cm (median value)		9 (3.5)	1.1 (0.6–2.2)	2.74 (0.74–10.12)	2.34 (0.62–8.87)
<1.76 cm		3 (1.2)	0.4 (0.1–1.3)	1 (reference)	1 (reference)
Absolute RVFWLS	528				
≥18.6% (median value)		4 (1.5)	0.5 (0.2–1.3)	0.40 (0.13–1.28)	0.44 (1.33–1.43)
<18.6%		10 (3.8)	1.3 (0.7–2.4)	1 (reference)	1 (reference)
PASP	489				
≥27.0 mm Hg (median value)		7 (2.9)	0.9 (0.4–1.9)	3.14 (0.65–15.13)	3.07 (0.63–14.94)
<27.0 mm Hg		2 (0.8)	0.3 (0.1–1.2)	1 (reference)	1 (reference)

No significant association between the other echocardiographic parameters (as shown in Table 4) and the composite renal outcome was found. EDA indicates end-diastolic area; eGFR, estimated glomerular filtration rate; ESA, end-systolic area; FAC, fractional area change; GLS, global longitudinal strain; HR, hazard ratio; LA, left atrium; LV, left ventricle; LVEDVi, LV end-diastolic volume index; LVEF, LV ejection fraction; LVESVi, LV end-systolic volume index; PASP, pulmonary artery systolic pressure; RV, right ventricle; RVFWLS, RV free wall longitudinal strain; SBP, systolic blood pressure; and TAPSE, tricuspid annular plane systolic excursion.

*Adjustment for age, SBP, diabetes, treatment arm, and baseline eGFR.

receptor antagonists (<30% of patients had this class of medication in our study) in HFpEF patients.

Conclusions

Among patients with HFpEF enrolled in the PARAGON-HF echocardiographic substudy, evidence of higher LV mass, altered LV structure, and deterioration of RV structure and function at baseline were individually associated with an increased risk of renal events, and higher LV mass and filling pressures predicted a more profound decline in kidney function. Beyond underscoring the close relationship between the heart and kidneys in patients with HF even when LVEF is preserved, our results suggest that assessing these parameters may help identify patients with HFpEF at higher risk for adverse renal events and may be considered as potential therapeutic targets.

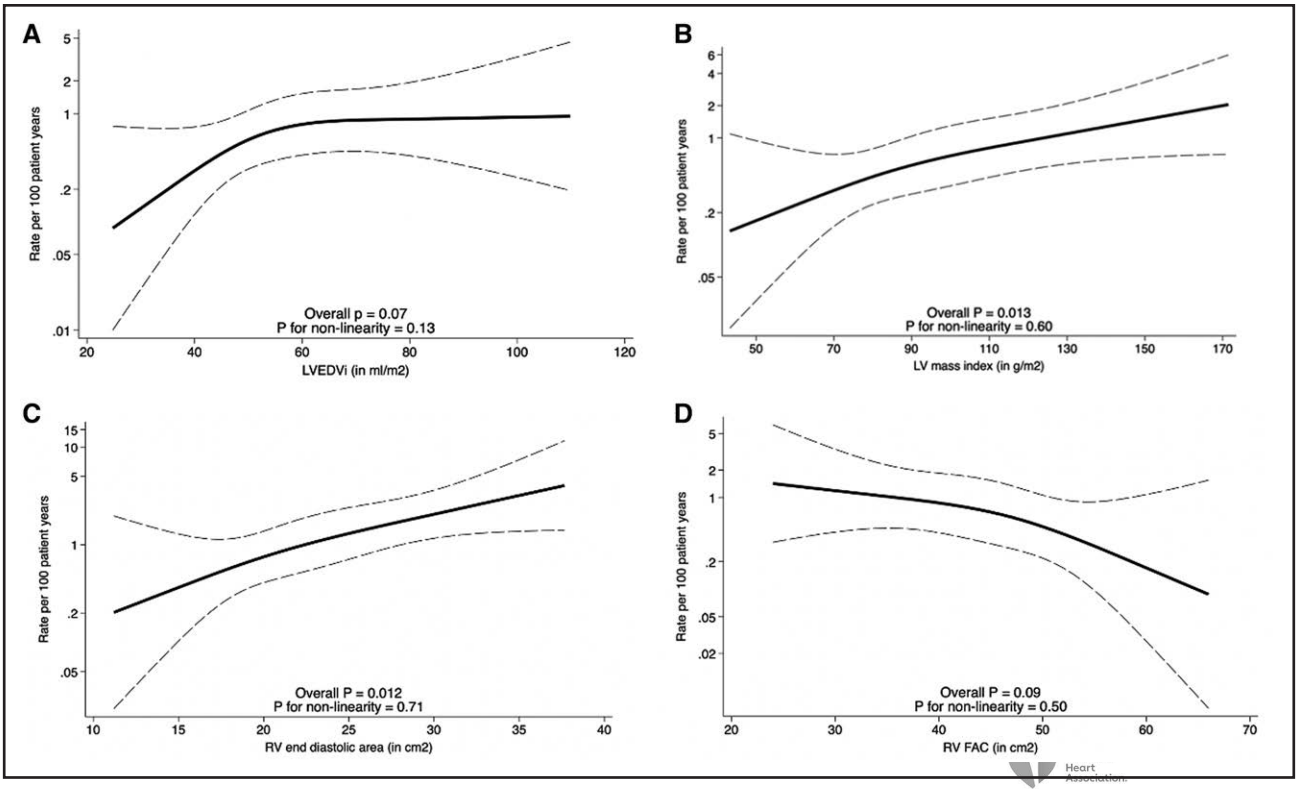

Figure 2. Risk-adjusted absolute incidence rates for the composite renal outcome across the range of LVEDVi, LV mass index, RV end-diastolic area, and RV FAC.

A, LVEDVi; **B**, LV mass index; **C**, RV end-diastolic area; and **D**, RV FAC. All echocardiographic parameters were measured at baseline. Adjustment for age, SBP, diabetes, treatment arm, and baseline eGFR. eGFR indicates estimated glomerular filtration rate; LV, left ventricle; LVEDVi, left ventricular end-diastolic volume index; RV, right ventricle; RV FAC, right ventricular fractional area change; and SBP, systolic blood pressure.

ARTICLE INFORMATION

Received April 24, 2024; accepted August 1, 2024.

Affiliations

Division of Cardiovascular Medicine, (H.L., S.C., S.L., M.A., A.K., K.K.T., B.L.C., N.P., X.W., M.A.P., S.M.H., S.D.S., H.S.) and Renal Division, Department of Medicine (F.R.M.C.), Brigham and Women's Hospital, Harvard Medical School, Boston, MA. Azienda Socio Sanitaria Territoriale Spedali Civili of Brescia, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Italy (R.M.I.). Division of Cardiovascular Medicine, University of Texas Southwestern Medical Center, Dallas (A.M.S.). Department of Cardiovascular Diseases, University of Zagreb School of Medicine, University Hospital Centre Zagreb, Croatia (M.C.). National Heart Centre Singapore and Duke-National University of Singapore, Singapore (C.S.P.L.). Department of Cardiology, Montreal Heart Institute, Université de Montréal, Québec, QC, Canada (E.O.). British Heart Foundation Glasgow Cardiovascular Research Centre, School of Cardiovascular and Metabolic Health, University of Glasgow, Scotland, United Kingdom (J.J.V.M.).

Sources of Funding

The Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor With Angiotensin-Receptor Blockers Global Outcomes in HF With Preserved Ejection Fraction trial was sponsored by Novartis.

Disclosures

Dr Lu received research funding from the Gottfried und Julia Bangerter-Rhyner Foundation, the SICPA (Société industrielle et commerciale de produits alimentaires) Foundation, and the Société Académique Vaudoise. Dr Chatur is supported by the Canadian Arthur J.E. Child's Cardiology Fellowship. Dr Mc Causland reports grant funding from the National Institutes of Health (NIH), Satellite Healthcare, Fifth Eye, Lexicon, and Novartis paid directly to his institution; consulting fees from GlaxoSmithKline (GSK) and Zydus Therapeutics; and expert witness fees from Rubin-Anders Scientific. Dr Shah reports consulting fees from Philips Ultrasound and research funds from Novartis through Brigham and Women's Hospital. He was supported by NIH/National Heart, Lung, and Blood Institute (NHLBI) grant K24HL152008. Dr Cikes reports Investigator-Initiated Research Grants to institution: Novartis, Abbott, and Pfizer; Clinical Study Contracts with institution: NovoNordisk and CorVia; advisory role and speaker honoraria, travel grants from Abbott, Abiomed, Amgen, Amicus Therapeutics, Astra Zeneca, Bayer, Boehringer Ingelheim, GE Healthcare, Livanova, Krka Pharma, Novartis, NovoNordisk, Pfizer, Pulsify Medical, Roche, Swixx, Takeda, Teva Pharmaceutical Industries, and Viatris. Dr Claggett reports personal consulting from Alnylam, Cardurion, Corvia, Cytokinetics, CVRX, Intellia, and Rocket. Dr Lam is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from NovoNordisk and Roche Diagnostics; has served as consultant or on the Advisory Board/Steering Committee (SC)/Executive Committee for Alleviant Medical, Allysta Pharma, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, CardioRenal, Cytokinetics, Darma Inc, EchoNous Inc, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen Research and Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Quidel Corporation, Radcliffe Group Ltd, Recardio Inc, ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and serves as cofounder and nonexecutive director of Us2.ai. Dr O'Meara reports grants/research support from the Montreal Heart Institute's Carolyn & Richard J. Renaud Chair for Research in Heart Failure, with fees paid through her institution for this Chair and for the following: Canadian Heart Function Alliance (CHFA) Team Grant, funded by the Canadian Institutes of Health Research (SC member), and involvement in the following trials as a SC member for DAPA ACT HF-TIMI 68 (Dapagliflozin and Effect on Cardiovascular Events in Acute Heart Failure–Thrombolysis in Myocardial Infarction 68; TIMI [Thrombolysis in Myocardial Infarction] group and AZ) and GARDEN-HF (A Study of Ponsegromab in People With Heart Failure; TIMI group and Pfizer), for HEART-FID (Ferric Carboxymaltose in Heart Failure With Iron Deficiency; SC member, American Regent), CARDINAL-HF (Effectiveness of CRD-740

in Heart Failure; SC member, Cardurion), and HERMES (Research Study to Look at How Ziltivekimab Works Compared to Placebo in People With Heart Failure and Inflammation; National Lead Investigator Novo Nordisk); reports consulting fees from Astra Zeneca, Boerhinger Ingelheim, GSK, Novartis, and Novo Nordisk; speaker fees from Astra Zeneca, Boerhinger Ingelheim, GSK, Novartis, Novo Nordisk, Pfizer, and other fees from Cytokinetics (Heart Failure Patient Steering Committee), industry partners for Canadian Heart Function Alliance Network. Dr Wang is supported by the Scott Schoen and Nancy Adams First.In.Women Cardiovascular Fellowship, Mary Horrigan Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital, and the American College of Cardiology/Association of Black Cardiologists Merck Research Fellowship Award. Dr McMurray reports payments through Glasgow University from work on clinical trials, consulting and other activities from: Amgen, AstraZeneca, Bayer, Cardurion, Cytokinetics, GSK, KBP Biosciences, and Novartis; personal consultancy fees from: Alnylam Pharma, Bayer, Bristol Myers Squibb (BMS), George Clinical PTY Ltd, Ionis Pharma, Novartis, Regeneron Pharma, River 2 Renal Corporation; reports the following lecture fees: Abbott, Alkem Metabolics, Astra Zeneca, Blue Ocean Scientific Solutions Ltd, Boehringer Ingelheim, Canadian Medical and Surgical Knowledge, Emcure Pharma Ltd, Eris Lifesciences, European Academy of Continuing Medical Education, Hikma Pharmaceuticals, Imagica health, Intas Pharma, J.B. Chemicals & Pharma Ltd, Lupin Pharma, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Sun Pharma, The Corpus, Translation Research Group, Translational Medicine Academy. He is a director of Global Clinical Trial Partners Ltd. Dr Pfeffer reports research grant support (via institution): Lexicon and Novartis. He is a consultant to Alnylam, AstraZeneca, Boehringer Ingelheim and Eli Lilly Alliance, DalCor, Lexicon, NHLBI Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies (Master Protocol Committee), Novartis, Novo Nordisk, and Sanofi, and has equity in DalCor. Dr Hegde reports fees paid to the institution for core laboratory services for BMS and Cytokinetics. Dr Solomon has received research grants from Alnylam, AstraZeneca, Bellerophon, Bayer, BMS, Cytokinetics, Eidos, Gossamer, GSK, Ionis, Lilly, MyoKardia, NIH/NHLBI, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, Us2.ai, and has consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boeringer-Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, and Valo. Dr Skali reports research support or consulting fees from: ABT Associates, Astellas Pharma, Emmi Solutions, and Hikma Pharmaceuticals. The other authors report no conflicts.

Supplemental Material

STROBE Checklist

REFERENCES

1. Gori M, Senni M, Gupta DK, Charytan DM, Kraigher-Krainer E, Pieske B, Claggett B, Shah AM, Santos ABS, Zile MR, et al; PARAMOUNT Investigators. Association between renal function and cardiovascular structure and function in heart failure with preserved ejection fraction. *Eur Heart J.* 2014;35:3442–3451. doi: 10.1093/eurheartj/ehu254
2. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J.* 2014;35:455–469. doi: 10.1093/eurheartj/eht386
3. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, Granger CB, Michelson EL, Ostergren J, Cornel JH, et al; Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Investigators. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation.* 2006;113:671–678. doi: 10.1161/CIRCULATIONAHA.105.580506
4. Mc Causland FR, Lefkowitz MP, Claggett B, Anavekar NS, Senni M, Gori M, Jhund PS, McGrath MM, Packer M, Shi V, et al. Angiotensin-neprilysin inhibition and renal outcomes in heart failure with preserved ejection fraction. *Circulation.* 2020;142:1236–1245. doi: 10.1161/CIRCULATIONAHA.120.047643
5. Mc Causland FR, Claggett BL, Vaduganathan M, Desai AS, Jhund P, de Boer RA, Docherty K, Fang J, Hernandez AF, Inzucchi SE, et al. Dapagliflozin and kidney outcomes in patients with heart failure with mildly reduced or preserved ejection fraction: a prespecified analysis of the DELIVER randomized clinical trial. *JAMA Cardiol.* 2023;8:56–65. doi: 10.1001/jamacardio.2022.4210
6. Packer M, Butler J, Zannad F, Pocock SJ, Filippatos G, Ferreira JP, Brueckmann M, Jamal W, Zeller C, Wanner C, et al; EMPEROR Study Group. Empagliflozin and major renal outcomes in heart failure. *N Engl J Med.* 2021;385:1531–1533. doi: 10.1056/NEJMc2112411
7. Mullens W, Damman K, Testani JM, Martens P, Mueller C, Lassus J, Tang WHW, Skouri H, Verbrugge FH, Orso F, et al. Evaluation of kidney function throughout the heart failure trajectory - a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2020;22:584–603. doi: 10.1002/ejhf.1697
8. Zannad F, Rossignol P. Cardiorenal syndrome revisited. *Circulation.* 2018;138:929–944. doi: 10.1161/CIRCULATIONAHA.117.028814
9. Unger ED, Dubin RF, Deo R, Daruwalla V, Friedman JL, Medina C, Beussink L, Freed BH, Shah SJ. Association of chronic kidney disease with abnormal cardiac mechanics and adverse outcomes in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail.* 2016;18:103–112. doi: 10.1002/ejhf.445
10. Verma A, Anavekar NS, Meris A, Thune JJ, Arnold JM, Ghali JK, Velazquez EJ, McMurray JJV, Pfeffer MA, Solomon SD. The relationship between renal function and cardiac structure, function, and prognosis after myocardial infarction: the VALIANT echo study. *J Am Coll Cardiol.* 2007;50:1238–1245. doi: 10.1016/j.jacc.2007.06.018
11. Matsushita K, Kwak L, Sang Y, Ballew SH, Skali H, Shah AM, Coresh J, Solomon S. Kidney disease measures and left ventricular structure and function: the atherosclerosis risk in communities study. *J Am Heart Assoc.* 2017;6:e006259. doi: 10.1161/JAHA.117.006259
12. Landler NE, Olsen FJ, Christensen J, Bro S, Feldt-Rasmussen BO, Hansen D, Kamper AL, Christoffersen C, Ballegaard ELF, Sørensen IMH, et al. Associations between albuminuria, estimated GFR and cardiac phenotype in a cohort with chronic kidney disease: the CPH-CKD ECHO study. *J Card Fail.* 2022;28:1615–1627. doi: 10.1016/j.cardfail.2022.09.002
13. Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B, Zile MR, Voors AA, Lefkowitz MP, Packer M, et al; PARAMOUNT Investigators. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. *J Am Coll Cardiol.* 2014;63:447–456. doi: 10.1016/j.jacc.2013.09.052
14. Inciardi RM, Abanda M, Shah A, Cikes M, Claggett B, Skali H, Vaduganathan M, Prasad N, Litwin S, Merkely B, et al. Right ventricular function and coupling to pulmonary circulation in heart failure with preserved ejection fraction: the PARAGON-HF trial. *J Am Coll Cardiol.* 2023;82:489. doi: 10.1016/j.jacc.2023.05.010
15. Inciardi RM, Bonelli A, Biering-Sorensen T, Cameli M, Pagnesi M, Lombardi CM, Solomon SD, Metra M. Left atrial disease and left atrial reverse remodelling across different stages of heart failure development and progression: a new target for prevention and treatment. *Eur J Heart Fail.* 2022;24:959–975. doi: 10.1002/ejhf.2562
16. Solomon SD, Rizkala AR, Gong J, Wang W, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, et al. Angiotensin receptor neprilysin inhibition in heart failure with preserved ejection fraction: rationale and design of the PARAGON-HF trial. *JACC Heart Fail.* 2017;5:471–482. doi: 10.1016/j.jchf.2017.04.013
17. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, et al; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med.* 2019;381:1609–1620. doi: 10.1056/NEJMoa1908655
18. Shah AM, Cikes M, Prasad N, Li G, Getchevski S, Claggett B, Rizkala A, Lukashevich I, O'Meara E, Ryan JJ, et al; PARAGON-HF Investigators. Echocardiographic features of patients with heart failure and preserved left ventricular ejection fraction. *J Am Coll Cardiol.* 2019;74:2858–2873. doi: 10.1016/j.jacc.2019.09.063
19. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2015;28:1–39.e14. doi: 10.1016/j.echo.2014.10.003
20. Shah AM, Shah SJ, Anand IS, Sweitzer NK, O'Meara E, Heitner JF, Sopko G, Li G, Assmann SF, McKinlay SM, et al; TOPCAT Investigators. Cardiac structure and function in heart failure with preserved ejection fraction: baseline findings from the echocardiographic study of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. *Circ Heart Fail.* 2014;7:104–115. doi: 10.1161/CIRCHEARTFAILURE.113.000887
21. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in

the presence of absence of asynergy. *Am J Cardiol*. 1976;37:7–11. doi: 10.1016/0002-9149(76)90491-4
22. Gorter TM, van Veldhuisen DJ, Bauersachs J, Borlaug BA, Celutkiene J, Coats AJS, Crespo-Leiro MG, Guazzi M, Harjola VP, Heymans S, et al. Right heart dysfunction and failure in heart failure with preserved ejection fraction: mechanisms and management. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2018;20:16–37. doi: 10.1002/ejhf.1029
23. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, Crews DC, Doria A, Estrella MM, Froissart M, et al; Chronic Kidney Disease Epidemiology Collaboration. New creatinine- and cystatin c-based equations to estimate GFR without race. *N Engl J Med*. 2021;385:1737–1749. doi: 10.1056/NEJMoa2102953
24. Vaduganathan M, Ferreira JP, Rossignol P, Neuen BL, Claggett BL, Pfeffer MA, McMurray JJV, Pitt B, Zannad F, Solomon SD. Effects of steroidal mineralocorticoid receptor antagonists on acute and chronic estimated glomerular filtration rate slopes in patients with chronic heart failure. *Eur J Heart Fail*. 2022;24:1586–1590. doi: 10.1002/ejhf.2635
25. Hughson MD, Puelles VG, Hoy WE, Douglas-Denton RN, Mott SA, Bertram JF. Hypertension, glomerular hypertrophy and nephrosclerosis: the effect of race. *Nephrol Dial Transplant*. 2014;29:1399–1409. doi: 10.1093/ndt/gft480
26. Heinzel FR, Hohendanner F, Jin G, Sedej S, Edelmann F. Myocardial hypertrophy and its role in heart failure with preserved ejection fraction. *J Appl Physiol (1985)*. 2015;119:1233–1242. doi: 10.1152/japplphysiol.00374.2015
27. Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. *Eur Heart J*. 2014;35:3452–3462. doi: 10.1093/eurheartj/ehu193
28. Van Aelst LNL, Arrigo M, Placido R, Akiyama E, Girerd N, Zannad F, Manivet P, Rossignol P, Badoz M, Sadoune M, et al. Acutely decompensated heart failure with preserved and reduced ejection fraction present with comparable haemodynamic congestion. *Eur J Heart Fail*. 2018;20:738–747. doi: 10.1002/ejhf.1050
29. Méndez AB, Azancot MA, Olivella A, Soler MJ. New aspects in cardiorenal syndrome and HFpEF. *Clin Kidney J*. 2022;15:1807–1815. doi: 10.1093/ckj/sfac133
30. Dini FL, Demmer RT, Simioniuc A, Morrone D, Donati F, Guarini G, Orsini E, Caravelli P, Marzilli M, Colombo PC. Right ventricular dysfunction is associated with chronic kidney disease and predicts survival in patients with chronic systolic heart failure. *Eur J Heart Fail*. 2012;14:287–294. doi: 10.1093/eurjhf/hfr176
31. Delgado C, Baweja M, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, Mendu ML, Miller WG, Moxey-Mims MM, Roberts GV, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN task force on reassessing the inclusion of race in diagnosing kidney disease. *Am J Kidney Dis*. 2022;79:268–288.e1. doi: 10.1053/j.ajkd.2021.08.003