KI REPORTS
KIReports.org
CLINICAL RESEARCH

Peak Tricuspid Regurgitation Jet Velocity and Kidney Outcomes in Patients With Heart Failure With Preserved Ejection Fraction

Tatsufumi Oka[1,2], Hocine Tighiouart[3,4], Wendy McCallum[1], Marcelle Tuttle[1], Jeffrey M. Testani[5] and Mark J. Sarnak[1]

[1]Division of Nephrology, Tufts Medical Center, Boston, Massachusetts, USA; [2]Department of Nephrology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan; [3]Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, Massachusetts, USA; [4]Tufts Clinical and Translational Science Institute, Tufts University, Boston, Massachusetts, USA; and [5]Division of Cardiovascular Medicine, Yale School of Medicine, New Haven, Connecticut, USA

Introduction: Although venous congestion secondary to elevated pulmonary artery pressure (PAP) has been hypothesized to worsen kidney function, the association of peak tricuspid regurgitation jet velocity (pTRV), a surrogate of PAP, with kidney outcomes remains uncertain in heart failure (HF) with preserved ejection fraction (HFpEF).

Methods: This *post hoc* analysis of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial analyzed participants with a left ventricular ejection fraction (LVEF) of ≥45% who had pTRV measured by echocardiography at baseline. For the cross-sectional analysis, the association of baseline pTRV with baseline estimated glomerular filtration rate (eGFR) was assessed using linear regression. For the longitudinal analysis, the association of baseline pTRV with decline in eGFR of ≥30% and doubling of serum creatinine was assessed using Cox proportional hazards models.

Results: Among 450 participants, the mean (SD) baseline age, LVEF, pTRV, and eGFR were 72.3 (9.6) years, 58.2% (7.4%), 2.8 (0.5) m/s, and 62.1 (18.7) ml/min per 1.73 m^2, respectively. Each 1 SD higher pTRV was associated with a lower baseline eGFR (coefficient, −1.79; 95% confidence interval [CI], −3.48 to −0.10 ml/min per 1.73 m^2). Over a median (interquartile range) follow-up of 3.0 (2.0–4.4) years, 203 (45%) patients experienced ≥30% eGFR decline, and 48 (11%) experienced creatinine doubling. Each 1 SD higher pTRV was associated with a 20% higher risk of ≥30% eGFR decline (hazard ratio [HR], 1.20; 95% CI, 1.04–1.39) and a 45% higher risk of creatinine doubling (HR, 1.45; 95% CI, 1.09–1.94).

Conclusions: Higher pTRV was associated with lower eGFR at baseline, and higher risk of ≥30% eGFR decline and creatinine doubling among patients with HFpEF.

Kidney Int Rep (2024) **9,** 3035–3044; https://doi.org/10.1016/j.ekir.2024.07.009
KEYWORDS: chronic kidney disease; heart failure with preserved ejection fraction; pulmonary hypertension; tricuspid regurgitation jet velocity; venous congestion

Kidney protection is an important treatment goal among patients with HFpEF because reduced GFR is associated with an increased risk of mortality and adverse cardiovascular events.[1-3] Plausible causes of reduced GFR in HFpEF are comorbid conditions, such as hypertension, diabetes mellitus (DM), and obesity.[4,5] Despite the availability of various guideline-recommended treatments for these comorbid conditions, chronic kidney disease (CKD) remains highly prevalent in patients with HFpEF, affecting approximately 50% to 60% of patients.[2,4,6,7] Therefore, identifying additional, and ideally modifiable, risk factors for CKD and kidney disease progression is of major importance in HFpEF.

Recent attention has been focused on the importance of assessing PAP among patients with HF because an increase in PAP is the earliest physiologic sign of decompensation.[8,9] In clinical settings, echocardiographic pTRV is used for screening for pulmonary hypertension (PH).[10] Previous studies have demonstrated an inverse association between pTRV and eGFR in cross-sectional analyses among patients with HF with reduced ejection fraction.[11,12] This may be

Correspondence: Tatsufumi Oka, Division of Nephrology, Tufts Medical Center, 800 Washington St, Boston, Massachusetts 02111, USA. E-mail: oka@kid.med.osaka-u.ac.jp

Received 23 March 2024; revised 1 July 2024; accepted 8 July 2024; published online 17 July 2024

consistent with an underlying pathophysiology wherein increased renal venous congestion secondary to elevated PAP, reflected by elevated pTRV, may predispose to kidney function decline. There are, however, few data about the relation between pTRV and longitudinal changes in kidney function in HF regardless of LVEF. We hypothesized that pTRV may be an additional risk factor for kidney function decline among patients with HFpEF.

In this study, we investigated the association of pTRV with kidney outcomes in both cross-sectional and longitudinal analysis of participants who underwent echocardiography at baseline in the TOPCAT trial.

METHODS

Study Design and Population

TOPCAT was an international, multicenter, randomized, placebo-controlled trial that investigated the efficacy and safety of spironolactone, a mineralocorticoid receptor antagonist, on cardiovascular outcomes among patients with HFpEF (NCT00094302).[13] Detailed trial methods have been described elsewhere.[14] In brief, adult patients (aged ≥50 years) with symptoms and signs of HF who had a LVEF of ≥45% and had either a history of HF hospitalization in the prior 12 months or an elevated natriuretic peptide (B-type natriuretic peptide of ≥100 pg/ml or N-terminal pro–B-type natriuretic peptide of ≥360 pg/ml) in the prior 60 days were enrolled. Controlled systolic blood pressure (BP) of <140 mm Hg or 140 to 160 mm Hg (if on ≥3 antihypertensive medications) and serum potassium of <5.0 mmol/l were required for eligibility. Key exclusion criteria included severe kidney dysfunction (eGFR of <30 ml/min per 1.73 m^2 or serum creatinine of ≥2.5 mg/dl), chronic pulmonary disease requiring home O_2 or oral steroid therapy, atrial fibrillation with a resting heart rate >90 bpm, and severe systemic illness with a life expectancy of <3 years. Participants were randomly assigned to either 15 mg/d of spironolactone or placebo in addition to standard HF therapies in a 1:1 ratio. Among a total of 3445 eligible patients, the present analysis was restricted to those who underwent echocardiography at baseline. The echocardiography procedure details were previously documented.[13,15] Briefly, for quality control purposes, each enrolling site was required to submit echocardiographic images from at least the first 2 randomized patients for quantification of LVEF by the echocardiography core laboratory at Brigham and Women's Hospital. At 27 sites, patients consenting to the overall TOPCAT trial were separately consented to participate in the echocardiographic substudy, where echocardiography was performed using a study-specific protocol at baseline. Among a combined total of 1017 baseline echo studies received from 204 sites, 935 studies were suitable for quantitative analysis. Of these 935 studies, 450 measured pTRV and were included in the present analysis (Supplementary Figure S1).

TOPCAT was conducted in accordance with the Declaration of Helsinki, and its protocol was approved by an institutional review committee at each site. All participants gave written informed consent before the enrollment; the present analysis was deemed exempt from review by the Tufts Health Sciences Institutional Review Board. The database was obtained via the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center.

Exposures of Interest

The exposure of interest in the present study was baseline echocardiographic pTRV (m/s), a recognized and noninvasive surrogate for PAP.[16-19] Image data, whether in digital or analog format, were transmitted to the echocardiography core laboratory at Brigham and Women's Hospital, where dedicated analysts, blinded to clinical information and the randomization group, performed all quantitative measures. The evaluations of tricuspid regurgitation as well as other quantitative measures were subsequently reviewed by an experienced echocardiographer.

Study Outcomes

The primary outcome of interest was a decline in eGFR of ≥30% from baseline because it is accepted as a surrogate end point in CKD trials.[20-22] eGFR was calculated using the 2021 CKD Epidemiology Collaboration creatinine equation.[23] The secondary outcome included the doubling of serum creatinine level from baseline, which is consistent with a prespecified safety outcome in the original trial,[13] and the annualized eGFR slope. The eGFR slope was estimated for each patient using a linear mixed effects model for time-dependent eGFR with random effect terms (slope and intercept) to account for individual patient variability.[24,25] These outcomes were ascertained using all available serum creatinine values, including both protocol-based and non–protocol-based measures, consistent with the original TOPCAT trial, where all creatinine measures were used for the outcome of doubling of serum creatinine.[13] The non–protocol-based measures were collected at 1 week after any change in the dosing of trial drugs (spironolactone or placebo), whether the dose was increased, decreased, or stopped.

Covariates

Covariates of interest included demographic, physical, and behavioral characteristics, echocardiographic measurements, comorbid conditions, medications, and randomization group. Race was classified as Black or others. Smoking history was categorized as ever or never. The New York Heart Association classification was categorized as 3 to 4 or 1 to 2. LVEF was measured at the local site by means of echocardiography or radionuclide ventriculography within 6 months before randomization and after any myocardial infarction or other event that would affect LVEF. Variables other than LVEF were ascertained at the baseline screening visit.[13] PH was defined as pTRV of >2.8 m/s, which was suggested as a cutoff value in the initial PH evaluation in the recent European Society of Cardiology/European Respiratory Society guideline.[10]

Statistical Analyses

Continuous variables were presented as means ± SD or medians and interquartile ranges as appropriate, and categorical variables were presented as numbers and percentages.

Baseline Cross-Sectional Analysis

The correlation between pTRV and eGFR was assessed using Pearson's correlation. pTRV was evaluated both as a continuous and categorical (quartile) to assess for nonlinear relations with outcomes. Linear and logistic regression models were used to relate pTRV with eGFR and CKD (defined as eGFR of <60 ml/min per 1.73 m^2), respectively. These models were adjusted for age, sex, race, body mass index, systolic BP, smoking history, the New York Heart Association classification, LVEF, comorbid conditions (DM and hypertension), and medications (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and diuretic agents). Randomization group was not included as a covariate because all the variables in the model were ascertained before the randomization.

Longitudinal Analysis

Kaplan-Meier survival was evaluated by pTRV quartiles. HRs for each outcome event were calculated, considering pTRV as both a continuous and categorical variable, using Cox proportional hazards regression models. These models were adjusted for baseline eGFR, randomization group, and the same covariates as those in the baseline analysis. Schoenfeld residuals were used to assess the proportional hazard assumption. The association of continuous or categorical pTRV with annualized eGFR slope was assessed using linear regression adjusted for the same covariates. In the categorical analyses, *P*-values for trend were obtained by treating the ordinal categorical variable as continuous.

Several sensitivity analyses were performed to assess the robustness of our main findings. Survival analysis was repeated, considering the following: (i) a Fine and Gray competing risk model with all-cause death as a competing event; (ii) ≥30% eGFR decline observed on at least 2 consecutive visits; (iii) ≥40% eGFR decline; (iv) a discrete-time survival model (approximated by logistic regression using person-time intervals) for ≥30% eGFR decline given that outcome events could only be ascertained at certain visit time points; (v) a Cox regression model for ≥30% eGFR decline, using eGFR values derived only from the protocol-based serum creatinine measures; and (vi) a survival analysis that was restricted to the TOPCAT-Americas (participants from the United States, Canada, Brazil, and Argentina) because there were significant regional differences in the clinical profiles, event rates, and study drug responses in TOPCAT, along with concerns about study conduct at the Russian and Georgian sites.[26,27]

Effect Modification

Effect modification was assessed by baseline age, sex, body mass index, LVEF, systolic BP, DM, and randomization group for the primary outcome of ≥30% eGFR decline. *P*-values for the interaction were computed by adding the interaction term to the multivariable Cox proportional hazards regression model in the primary analysis.

Statistical tests were 2-tailed, with significance set at $P < 0.05$. All statistical analyses were performed using Stata/IC (version 14.0; Stata Corp LLC) software.

RESULTS

Study Population and Patient Characteristics

A total of 450 patients were included in the analysis, of whom 225 (50%) were assigned to the treatment (spironolactone) group (Supplementary Figure S1). At baseline, the mean (SD) age, LVEF, pTRV, and eGFR were 72.3 (9.6) years, 58.2% (7.4%), 2.8 (0.5) m/s, and 62.1 (18.7) ml/min per 1.73 m^2, respectively (Table 1). Forty-six percent were men, 42% had a New York Heart Association classification of 3 to 4, and 92% had a history of hypertension. The prevalence of CKD and PH were 46% and 43%, respectively. Patients in higher quartiles of pTRV were older, more frequently female, and more likely to receive diuretic therapy, and they exhibited lower baseline eGFR. The prevalence of DM, systolic BP, and LVEF, were comparable across the pTRV quartiles. Patients included in the present analysis were older, more likely to be female, of Black race, had New York Heart Association class 3 to 4, and

Table 1. Patient characteristics at baseline stratified by quartiles of peak tricuspid regurgitation jet velocity

Characteristics	Total (N = 450)	Quartile 1 (n = 113)	Quartile 2 (n = 112)	Quartile 3 (n = 113)	Quartile 4 (n = 112)	P-value for trend
Demographic, physical, and behavioral characteristics						
Age, yr	72.3 ± 9.6	70.2 ± 9.2	71.8 ± 9.0	72.6 ± 10.4	74.6 ± 9.5	<0.001
Sex (Male)	206 (45.8%)	67 (59.3%)	42 (37.5%)	53 (46.9%)	44 (39.3%)	0.016
Black race	76 (16.9%)	19 (16.8%)	15 (13.4%)	18 (15.9%)	24 (21.4%)	0.303
BMI, kg/m^2	32.7 ± 7.9	33.1 ± 7.6	31.8 ± 7.4	33.0 ± 8.3	32.7 ± 8.2	0.967
Systolic BP, mm Hg	125.6 ± 15.5	125.4 ± 14.8	124.5 ± 15.7	127.3 ± 16.3	125.2 ± 15.3	0.723
NYHA classification 3–4	190 (42.4%)	45 (39.8%)	43 (38.7%)	51 (45.1%)	51 (45.6%)	0.237
Smoking history	240 (53.3%)	68 (60.2%)	50 (44.6%)	59 (52.2%)	63 (56.3%)	0.835
Echocardiography						
LVEF, %	58.2 ± 7.4	57.5 ± 7.2	58.3 ± 7.1	57.4 ± 7.4	59.5 ± 8.0	0.127
pTRV, m/s	2.8 ± 0.5	2.3 ± 0.1	2.6 ± 0.1	2.9 ± 0.1	3.4 ± 0.3	N/A
Comorbid conditions						
Hypertension	412 (91.6%)	107 (94.7%)	101 (90.2%)	99 (87.6%)	105 (93.8%)	0.640
Diabetes mellitus	178 (39.6%)	49 (43.4%)	35 (31.3%)	42 (37.2%)	52 (46.4%)	0.469
CKD[a]	208 (46.2%)	43 (38.1%)	41 (36.6%)	58 (51.3%)	66 (58.9%)	<0.001
PH[b]	193 (42.9%)	0 (0.0%)	0 (0.0%)	81 (71.7%)	112 (100.0%)	<0.001
Kidney function						
Creatinine, mg/dl	1.10 (0.90, 1.40)	1.10 (0.92, 1.30)	1.00 (0.81, 1.29)	1.10 (0.96, 1.40)	1.20 (0.97, 1.40)	0.133
eGFR, ml/min per 1.73 m^2	62.1 ± 18.7	64.7 ± 18.2	66.0 ± 18.5	60.6 ± 19.6	57.0 ± 17.3	<0.001
Medications						
ACEI/ARB	354 (78.7%)	88 (77.9%)	91 (81.3%)	89 (78.8%)	86 (76.8%)	0.741
Diuretic agents	396 (88.0%)	94 (83.2%)	95 (84.8%)	99 (87.6%)	108 (96.4%)	0.002
Randomization group						
Spironolactone	225 (50.0%)	47 (41.6%)	64 (57.1%)	52 (46.0%)	62 (55.4%)	0.152

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PH, pulmonary hypertension; pTRV, peak tricuspid regurgitation jet velocity.
[a]CKD was defined as baseline eGFR of <60 ml/min per 1.73 m^2.
[b]PH was defined as pTRV of >2.8 m/s.
Data are presented as means ± SD or medians (IQRs) for continuous variables and as numbers (percentages) for categorical variables.

exhibited lower eGFR at baseline compared to the rest of the participants in TOPCAT. LVEFs were similar between the groups (Supplementary Tables S1 and S2).

Baseline Cross-Sectional Analysis

At baseline, there was a significant negative correlation between pTRV and eGFR (r = −0.158, P <0.001) (Figure 1). In multivariable linear regression, each 1 SD higher pTRV was associated with a lower baseline eGFR (coefficient, −1.79; 95% CI, −3.48 to −0.10 ml/min per 1.73 m^2) (Table 2). Similar findings were observed when pTRV was analyzed as a categorical variable. Higher pTRV quartiles were associated with lower baseline eGFRs (P-value for trend of 0.023). Higher pTRV was also associated with a higher prevalence of CKD in both continuous and categorical analyses (Supplementary Table S3).

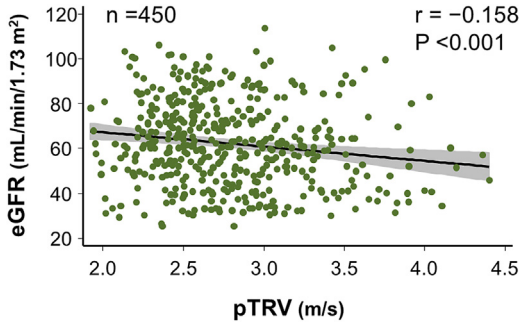

Figure 1. Correlation between baseline peak tricuspid regurgitation jet velocity and eGFR. Pearson's correlation was used. Shaded area represents 95% CI. CI, confidence interval; eGFR, estimated glomerular filtration rate.

Longitudinal Analysis

Over a median (interquartile range) follow-up of 3.0 (2.0–4.4) years, 203 patients (45%) experienced ≥30% decline in eGFR, 48 (11%) experienced doubling of creatinine, and 95 (21%) died. Kaplan-Meier curves showed higher incidence of ≥30% eGFR decline in higher pTRV quartiles (Figure 2). Higher pTRV quartiles were significantly associated with a higher risk of ≥30% eGFR decline (P-value for trend of 0.044) and creatinine doubling (P-value for trend of 0.048) in multivariable analyses (Table 3). Similarly, each 1 SD higher pTRV was associated with a 20% higher risk of ≥30% eGFR decline (HR, 1.20; 95% CI, 1.04–1.39) and a 45%-higher risk of creatinine doubling (HR, 1.45; 95% CI, 1.09–1.94). There were no significant interactions by age, sex, body mass index, LVEF, systolic BP, DM, and randomization group (Figure 3). The

Table 2. Association of baseline peak tricuspid regurgitation jet velocity with eGFR

	Continuous		Categorical				
			Coefficient (95% CI), ml/min per 1.73 m^2				*P* for trend
Outcome: eGFR	Coefficient (95% CI), ml/min per 1.73 m^2 (per 1 SD[a] higher pTRV)	*P*-value	Quartile 1[b]	Quartile 2[b]	Quartile 3[b]	Quartile 4[b]	
Model 1	−2.95 (−4.66 to −1.23)	0.001	Ref.	1.33 (−3.49 to 6.15)	−4.11 (−8.92 to 0.70)	−7.67 (−12.49 to −2.85)	<0.001
Model 2	−2.09 (−3.80 to −0.39)	0.016	Ref.	2.62 (−2.14 to 7.38)	−2.72 (−7.44 to 2.01)	−5.16 (−9.97 to −0.34)	0.007
Model 3	−1.79 (−3.48 to −0.10)	0.038	Ref.	0.98 (−3.66 to 5.62)	−3.29 (−7.87 to 1.30)	−4.32 (−9.05 to 0.41)	0.023

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; pTRV, peak tricuspid regurgitation jet velocity; Ref., reference.
[a]SD of pTRV is 0.5 m/s.
[b]Quartiles of pTRV at baseline.
Model 1. unadjusted model.
Model 2. adjustment for age and sex.
Model 3. model 2 + adjustment for race, BMI, systolic BP, smoking history, NYHA classification, LVEF, DM, hypertension, ACEI/ARB, and diuretic agents.

highest quartile of pTRV (vs. the lowest quartile) was significantly associated with 0.94 (95% CI, −1.85 to −0.03) ml/min per 1.73 m^2-faster annualized eGFR decline (Table 4). Consistent results were observed when pTRV was treated as a continuous variable.

Sensitivity analyses for the most part yielded consistent associations with the primary analyses. The association of pTRV with ≥30% eGFR decline or doubling of creatinine was consistent when all-cause death was used as a competing event (Supplementary Table S4). Higher pTRV was significantly associated both with higher risk of ≥30% eGFR decline in 2 consecutive visits (Supplementary Table S5) and with ≥40% eGFR decline (Supplementary Table S6). A Cox regression analysis using eGFR values derived only from the protocol-based serum creatinine measures yielded an effect size of pTRV that was directionally consistent but attenuated (Supplementary Table S7). A discrete-time survival analysis did not change the result substantially (Supplementary Table S8), neither did a Cox regression analysis restricted to the TOPCAT-Americas (Supplementary Table S9).

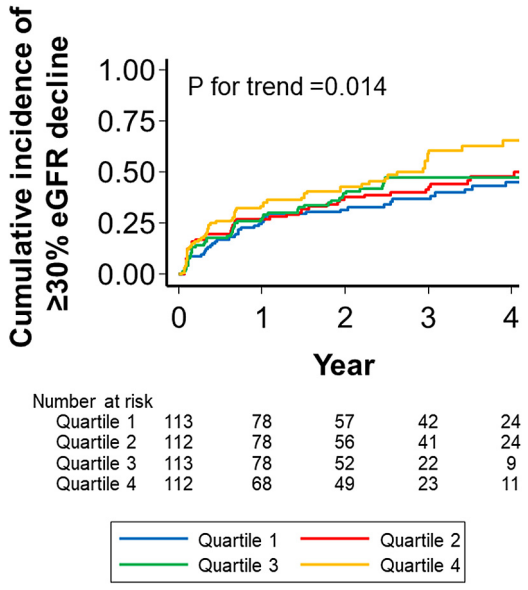

Figure 2. Kaplan-Meier curves for the incidence of ≥30% eGFR decline stratified by quartiles of peak tricuspid regurgitation jet velocity. eGFR, estimated glomerular filtration rate.

DISCUSSION

The present *post hoc* analysis examined the association of pTRV with kidney outcomes among patients with HFpEF enrolled in TOPCAT. Even after adjustment for potential confounders, higher pTRV was associated with lower eGFR at baseline. Higher pTRV was also associated with a higher risk of ≥30% eGFR decline and creatinine doubling, as well as a greater negative annualized eGFR slope. There were no significant interactions by age, sex, body mass index, LVEF, systolic BP, DM, and randomization group. These results suggest that pTRV is a risk factor for kidney function decline independent of conventional risk factors, such as obesity, hypertension, and DM, among patients with HFpEF.[4,5]

pTRV is an echocardiographic measure used to calculate the tricuspid regurgitant pressure gradient with the simplified Bernoulli equation (tricuspid regurgitant pressure gradient = 4 × $[pTRV]^2$).[28] Physiologically, systolic PAP equals right ventricular systolic pressure in the absence of a right ventricular outflow gradient, and thus can be estimated by adding the pTRV-derived tricuspid regurgitant pressure gradient to the estimated right atrial pressure (RAP) obtained from the size and distensibility of the inferior vena cava.[28–30] Because of potential inaccuracies in estimation of RAP using this method, the recent European Society of Cardiology/European Respiratory Society guidelines recommend using pTRV alone in the initial evaluation of PH, whereas right heart catheterization is the gold standard for diagnosing and classifying PH.[10,28] Taken together with the present results, we speculate that baseline systolic PAP may be associated with baseline kidney function and subsequent kidney function decline.

Several explanations can be proposed for the association of high pTRV with worse kidney outcomes.

Table 3. Association of baseline peak tricuspid regurgitation jet velocity with ≥30% decline in eGFR and doubling of creatinine

Outcome: ≥30% eGFR decline (N events = 203)	Continuous		Categorical				
			Hazard ratio (95% CI)				
	Hazard ratio (95% CI) (per 1 SD[a] higher pTRV)	*P*-value	Quartile 1[b] (*n* events = 44)	Quartile 2[b] (*n* events = 49)	Quartile 3[b] (*n* events = 51)	Quartile 4[b] (*n* events = 59)	*P* for trend
Model 1	1.21 (1.06–1.39)	0.005	Ref.	1.16 (0.77–1.75)	1.30 (0.87–1.95)	1.61 (1.09–2.38)	0.014
Model 2	1.20 (1.05–1.38)	0.009	Ref.	1.13 (0.74–1.70)	1.27 (0.85–1.92)	1.55 (1.04–2.32)	0.026
Model 3	1.20 (1.04–1.39)	0.013	Ref.	1.07 (0.70–1.64)	1.29 (0.85–1.96)	1.47 (0.97–2.22)	0.044
Outcome: Cr doubling (N events = 48)	**Continuous**		**Categorical**				
			Hazard ratio (95% CI)				
	Hazard ratio (95% CI) (per 1 SD[a] higher pTRV)	*P*-value	Quartile 1[b] (*n* events = 11)	Quartile 2[b] (*n* events = 6)	Quartile 3[b] (*n* events = 14)	Quartile 4[b] (*n* events = 17)	*P* for trend
Model 1	1.36 (1.04–1.77)	0.023	Ref.	0.52 (0.19–1.40)	1.37 (0.62–3.03)	1.67 (0.78–3.57)	0.051
Model 2	1.40 (1.07–1.83)	0.013	Ref.	0.52 (0.19–1.42)	1.41 (0.63–3.12)	1.83 (0.84–3.98)	0.031
Model 3	1.45 (1.09–1.94)	0.012	Ref.	0.55 (0.20–1.53)	1.34 (0.60–3.00)	1.79 (0.81–3.95)	0.048

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CI, confidence interval; Cr, creatinine; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; pTRV, peak tricuspid regurgitation jet velocity; Ref., reference.
[a]SD of pTRV is 0.5 m/s.
[b]Quartiles of pTRV at baseline.
Model 1. unadjusted model.
Model 2. adjustment for age and sex.
Model 3. Model 2 + adjustment for race, BMI, systolic BP, smoking history, NYHA classification, LVEF, DM, hypertension, ACEI/ARB, diuretic agents, baseline eGFR, and randomization group.

First, increased venous congestion secondary to elevated systolic PAP could predispose individuals to kidney damage. PH, primarily due to elevated left-side filling pressures,[29,31,32] is prevalent among patients with HFpEF, with observed prevalence ranging from 35% to 83%.[10,15,29,31] In theory, when PH is present, the right heart attempts to compensate for elevated PAP by balancing preload and afterload, potentially leading to venous congestion, particularly as the right ventricle begins to fail.[33] Venous congestion can

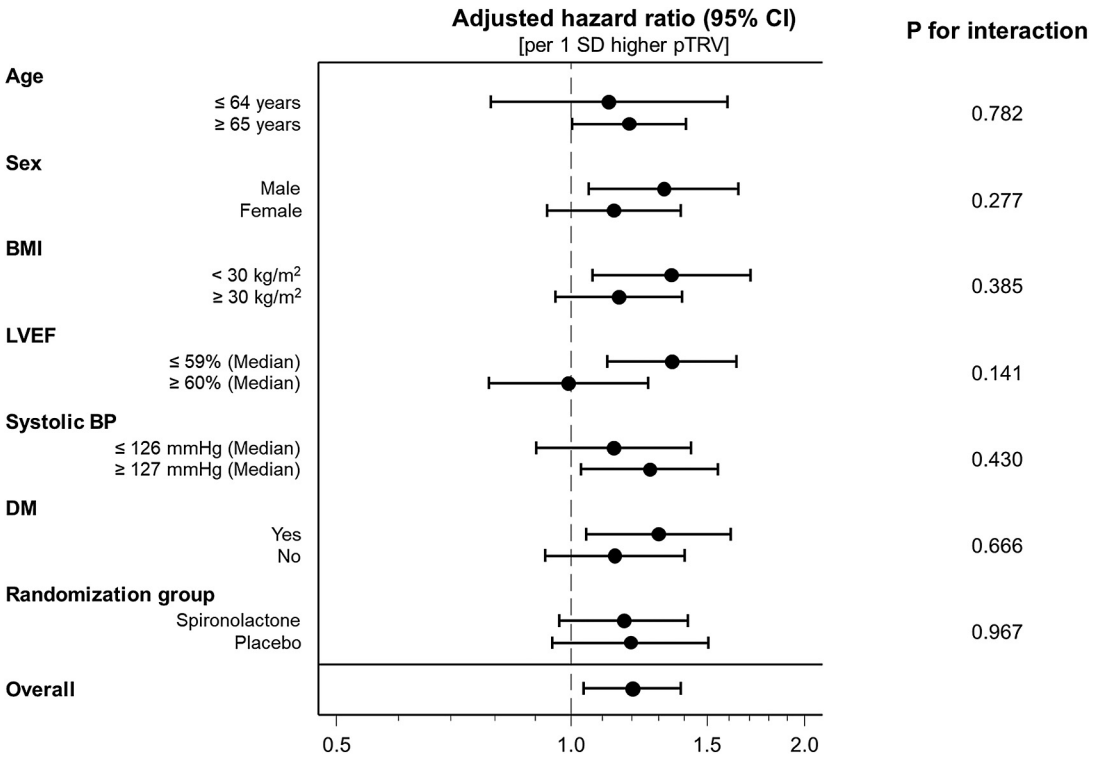

Figure 3. Associations of peak tricuspid regurgitation jet velocity with ≥30% eGFR decline in different subgroups of patients. Effect modification was assessed by baseline age, sex, BMI, LVEF, systolic BP, DM, and randomization group regarding the association between pTRV and ≥30% eGFR decline. *P*-values for the interaction were computed by adding the interaction term to the multivariable Cox proportional hazards regression model in the primary analysis. BMI, body mass index; BP, blood pressure, DM, diabetes mellitus; LVEF, left ventricular ejection fraction.

Table 4. Association of baseline peak tricuspid regurgitation jet velocity with annualized eGFR slope

	Continuous		Categorical				
			Coef. (95% CI) (ml/min per 1.73 m^2/yr)				
Outcome: annualized eGFR slope	Coef. (95% CI) (ml/min per 1.73 m^2/yr) (per 1 SD[a] higher pTRV)	*P*-value	Quartile 1[b]	Quartile 2[b]	Quartile 3[b]	Quartile 4[b]	*P* for trend
Model 1	−0.42 (−0.74 to −0.11)	0.009	Ref.	0.11 (−0.76 to 0.99)	−0.87 (−1.72 to −0.01)	−0.88 (−1.76 to −0.01)	0.011
Model 2	−0.41 (−0.72 to −0.09)	0.011	Ref.	0.10 (−0.77 to 0.97)	−0.86 (−1.72 to −0.01)	−0.85 (−1.73 to 0.02)	0.013
Model 3	−0.47 (−0.81 to −0.13)	0.006	Ref.	0.05 (−0.86 to 0.96)	−0.97 (−1.88 to −0.06)	−0.94 (−1.85 to −0.03)	0.009

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CI, confidence interval; Cr, creatinine; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; pTRV, peak tricuspid regurgitation jet velocity; Ref., reference.
[a]SD of pTRV is 0.5 m/s.
[b]Quartiles of pTRV at baseline.
Model 1. unadjusted model.
Model 2. adjustment for age and sex.
Model 3. Model 2 + adjustment for race, BMI, systolic BP, smoking history, NYHA classification, LVEF, DM, hypertension, ACEI/ARB, diuretic agents, baseline eGFR, and randomization group.

decrease trans glomerular pressure gradient,[34] induce renal parenchymal hypoxia due to elevated interstitial pressure,[35] and activate the renin-angiotensin-aldosterone system,[36] consequently leading to kidney function decline. Consistent with this hypothesis, previous studies have shown correlations between RAP and eGFR or CKD that were stronger than the relation between cardiac index and eGFR in World Health Organization group 1 PH[37] or decompensated HF with reduced ejection fraction.[38] Another potential explanation is that higher pTRV reflects more severe HFpEF which in turn may decrease renal plasma flow. In HFpEF, ventricular and arterial stiffness are increased, which may lead to a decrease in left ventricular filling pressure, stroke volume, and renal plasma flow, particularly under conditions such as vasodilator use, exercise, and low BP.[39–41] Decreased renal plasma flow may exacerbate kidney function by activating the renin-angiotensin-aldosterone and sympathetic nervous systems.[42]

Our present findings suggest the potential value of assessing pTRV, a noninvasive surrogate of systolic PAP, among ambulatory patients with HFpEF, for kidney prognosis. Although our analysis does not evaluate longitudinal changes in pTRV, there is a possibility that longitudinal changes may affect kidney prognosis, and monitoring pTRV and incorporation of therapeutic interventions that reduce pTRV may slow progression of CKD. Importantly, increasing attention has been focused on the importance of monitoring PAP among patients with HF regardless of their LVEF because an increase in PAP is an early physiologic sign of decompensation preceding increases in body weight, BP, or symptoms.[8,9] In a subgroup analysis of the CHAMPION trial among patients with HFpEF, HF management guided by PAP using the CardioMEMS sensor, an implantable PAP monitoring system, was associated with a 46% lower rate of HF hospitalization compared with conventional management.[43] Unfortunately, no data are available for kidney outcomes using this device.

To the best of our knowledge, the present study is the first to demonstrate the relation between an index of right filling pressure and longer-term kidney prognosis among patients with HFpEF. Strengths of the study include an international, multicenter, randomized, placebo-controlled trial with rigorous data collection and follow-up procedures, and consistent results in cross-sectional and longitudinal analyses. We performed adjustment for various potential confounders and confirmed the consistency of the association through subgroup and sensitivity analyses. This study is novel and suggests the potential in future studies of assessing pTRV, a surrogate of PAP, among patients with HFpEF from the perspective of prognosis and treatment.

This study has some limitations. First, the direct causal relation between pTRV and kidney outcomes cannot be proven, because of the observational nature of the study. Despite the adjustment for various covariates and subgroup analysis, the presence of residual confounding by measured and unmeasured covariates remains possible. For example, our survival analysis did not account for the confounding effects of longitudinal changes in the dosing of loop or thiazide diuretic agents. Up-titration of these drugs during follow-up, potentially more frequent in those with higher pTRV, may have resulted in further decline in eGFR, and therefore contributed to the association between pTRV and kidney outcomes. In addition, analyses that incorporate nonprotocol-based measures of serum creatinine resulted in a stronger relation of pTRV with decline in eGFR, and therefore potentially biased the strength of the association. Second, though pTRV is widely used as a useful surrogate for PAP in clinical and research settings, its diagnostic performance is modest[44,45] because it reflects tricuspid regurgitant pressure gradient and cannot perfectly reflect systolic PAP without considering RAP. Right heart catheterization or any other estimate of RAP was

not performed in TOPCAT. Therefore, we acknowledge that patients with significantly elevated right-sided filling pressure may have a substantial underestimation of their PAP estimated by pTRV. However, the prevalence of pTRV-defining PH in our cohort (42.9%) was consistent with findings from other HFpEF trials,[46–48] confirming the high prevalence of PH in HFpEF. Further studies are warranted to reproduce the present association with kidney outcomes using PAP obtained by right heart catheterization as an exposure variable. Third, the effect of longitudinal changes in pTRV on kidney outcomes was not addressed in the present analysis. Fourth, our main results were derived from the data of all pTRV-available participants in TOPCAT, including those at Russian or Georgian sites, where concern regarding study conduct has been raised. However, excluding these participants from the analysis did not change the results substantially. Finally, because TOPCAT mostly enrolled White and Black participants, and given the differences in baseline characteristics between those included in the present analysis in comparison with all participants in TOPCAT, the results may not be generalizable to all patients with HFpEF or to the entire TOPCAT population.

In summary, higher pTRV was associated with lower eGFR at baseline, higher risks of ≥30% eGFR decline and creatinine doubling, and greater negative annualized eGFR slope. These associations remained significant after multivariable adjustment. The results suggest the potential value of assessing echocardiographic pTRV, a noninvasive surrogate of pulmonary pressures, among patients with HFpEF from the perspective of kidney prognosis, which is consistent with recent attention focusing on PAP for the management of HF.[8,9,43] Additional and larger studies are needed to confirm these relations and to identify if monitoring pTRV and potential intervention to decrease pTRV, will slow progression of CKD in HFpEF.

DISCLOSURE

TO received research support from Osaka Medical Research Foundation for Intractable Diseases and Fukuda Foundation for Medical Technology. JMT reports grants and/or personal fees from 3ive labs, Bayer, Bristol Myers Squibb, Astra Zeneca, Novartis, Cardionomic, MagentaMed, Reprieve inc., FIRE1, W.L. Gore, Sanofi, Sequana Medical, Otsuka, Abbott, Merck, Windtree Therapeutics, Lexicon pharmaceuticals, Precardia, Relypsa, Regeneron, BD, Edwards life sciences, and Lilly. In addition, JMT has a patent for the treatment of diuretic resistance issued to Yale and Corvidia Therapeutics Inc, a patent method for measuring renalase issued to Yale, and a patent for the treatment of diuretic resistance pending with Reprieve inc. MJS serves on the steering committee for Akebia; received consulting fees from Boehringer Ingelheim; and has a spouse who works for Eli Lilly. All the other authors declared no competing interests.

ACKNOWLEDGMENTS

The TOPCAT trial was a randomized controlled trial and registered at ClinicalTrials.gov

(NCT00094302). This manuscript was prepared using TOPCAT research materials obtained from the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the TOPCAT or the National Heart, Lung, and Blood Institute.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DATA AVAILABILITY STATEMENT

Deidentified data created for the study will be available upon request to the principal investigator after proposals for collaboration or data sharing have been reviewed.

AUTHOR CONTRIBUTIONS

TO and MJS designed the study. TO, HT, WM, MT, JMT, and MJS obtained the data. TO and HT analyzed the data. JMT and MJS supervised the study. All the authors participated in data interpretation. TO drafted the manuscript. All the authors revised the manuscript and approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Flow diagram of the study.

Table S1. Comparison of characteristics between included and excluded participants.

Table S2. Comparison of those with and without peak tricuspid regurgitation jet velocity assessment in those who underwent echocardiography.

Table S3. Association of baseline peak tricuspid regurgitation jet velocity with prevalent chronic kidney disease.

Table S4. Association of baseline peak tricuspid regurgitation jet velocity with ≥30% decline in eGFR and doubling of creatinine using all-cause death as a competing event.

Table S5. Association of baseline peak tricuspid regurgitation jet velocity with ≥30% decline in eGFR in 2 consecutive visits.

Table S6. Association of baseline peak tricuspid regurgitation jet velocity with ≥40% decline in eGFR.

Table S7. Association of baseline peak tricuspid regurgitation jet velocity with ≥30% decline in eGFR derived only from protocol-based serum creatinine measures.

Table S8. Association of baseline peak tricuspid regurgitation jet velocity with ≥30% decline in eGFR in a discrete-time survival model.

Table S9. Association of baseline peak tricuspid regurgitation jet velocity with ≥30% decline in eGFR in TOPCAT participants from the Americas.

Check List.

REFERENCES

1. Shah SJ, Katz DH, Selvaraj S, et al. Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation*. 2015;131:269–279. https://doi.org/10.1161/CIRCULATIONAHA.114.010637
2. Beldhuis IE, Myhre PL, Claggett B, et al. Efficacy and safety of spironolactone in patients with HFpEF and chronic kidney disease. *JACC Heart Fail*. 2019;7:25–32. https://doi.org/10.1016/J.JCHF.2018.10.017
3. Ferreira JP, Claggett BL, Liu J, et al. Serum potassium and outcomes in heart failure with preserved ejection fraction: a post-hoc analysis of the Paragon-HF trial. *Eur J Heart Fail*. 2021;23:776–784. https://doi.org/10.1002/ejhf.2134
4. Joslin JR, Lioudaki E, Androulakis E. Interrelation between heart failure with preserved ejection fraction and renal impairment. *Rev Cardiovasc Med*. 2022;23:69. https://doi.org/10.31083/j.rcm2302069
5. Méndez AB, Azancot MA, Olivella A, Soler MJ. New aspects in cardiorenal syndrome and HFpEF. *Clin Kidney J*. 2022;15:1807–1815. https://doi.org/10.1093/ckj/sfac133
6. Tromp J, Teng TH, Tay WT, et al. Heart failure with preserved ejection fraction in Asia. *Eur J Heart Fail*. 2019;21:23–36. https://doi.org/10.1002/EJHF.1227
7. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381:1609–1620. https://doi.org/10.1056/NEJMOA1908655
8. Zile MR, Bennett TD, Sutton MSJ, et al. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation*. 2008;118:1433–1441. https://doi.org/10.1161/CIRCULATIONAHA.108.783910
9. Adamson PB. Pathophysiology of the transition from chronic compensated and acute decompensated heart failure: new insights from continuous monitoring devices. *Curr Heart Fail Rep*. 2009;6:287–292. https://doi.org/10.1007/s11897-009-0039-z
10. Humbert M, Kovacs G, Hoeper MM, et al. ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension developed by the task force for the diagnosis and treatment of (ESC) and the European Respiratory Society (ERS). *Eur Heart J*. 2022;43:3618–3731. https://doi.org/10.1093/eurheartj/ehac237
11. Jeevanandam V, Russell H, Mather P, Furukawa S, Anderson A, Raman J. Donor tricuspid annuloplasty during orthotopic heart transplantation: long-term results of a prospective controlled study. *Ann Thorac Surg*. 2006;82:2089–2095. https://doi.org/10.1016/J.ATHORACSUR.2006.07.014
12. Maeder MT, Holst DP, Kaye DM. Tricuspid regurgitation contributes to renal dysfunction in patients with heart failure. *J Card Fail*. 2008;14:824–830. https://doi.org/10.1016/j.cardfail.2008.07.236
13. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383–1392. https://doi.org/10.1056/NEJMoa1313731
14. Desai AS, Lewis EF, Li R, et al. Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. *Am Heart J*. 2011;162:966–972.e10. https://doi.org/10.1016/J.AHJ.2011.09.007
15. Shah AM, Claggett B, Sweitzer NK, et al. 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 (TOPCAT) trial. *Circ Heart Fail*. 2014;7:740–751. https://doi.org/10.1161/CIRCHEARTFAILURE.114.001583
16. Berger M, Haimowitz A, Tosh AV, Berdoff RL, Goldberg E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. *J Am Coll Cardiol*. 1985;6:359–365. https://doi.org/10.1016/S0735-1097(85)80172-8
17. Currie PJ, Seward JB, Chan KL, et al. Continuous wave Doppler determination of right ventricular pressure: a simultaneous Doppler-catheterization study in 127 patients. *J Am Coll Cardiol*. 1985;6:750–756. https://doi.org/10.1016/S0735-1097(85)80477-0
18. McQuillan BM, Picard MH, Leavitt M, Weyman AE. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation*. 2001;104:2797–2802. https://doi.org/10.1161/HC4801.100076
19. McNamara MJ, Sayanlar JJ, Dooley DJ, Srichai MB, Taylor AJ. A randomized pilot study on the effect of niacin on pulmonary arterial pressure. *Trials*. 2015;16:530. https://doi.org/10.1186/s13063-015-1013-6
20. Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA*. 2014;311:2518–2531. https://doi.org/10.1001/JAMA.2014.6634
21. Levey AS, Inker LA, Matsushita K, et al. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. *Am J Kidney Dis*. 2014;64:821–835. https://doi.org/10.1053/J.AJKD.2014.07.030
22. Inker LA, Lambers Heerspink HJ, Mondal H, et al. GFR decline as an alternative end point to kidney failure in clinical trials: a meta-analysis of treatment effects from 37 randomized trials. *Am J Kidney Dis*. 2014;64:848–859. https://doi.org/10.1053/J.AJKD.2014.08.017
23. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race.

N Engl J Med. 2021;385:1737–1749. https://doi.org/10.1056/NEJMOA2102953

24. Grams ME, Sang Y, Ballew SH, et al. Evaluating glomerular filtration rate slope as a surrogate end point for ESKD in clinical trials: an individual participant meta-analysis of observational data. *J Am Soc Nephrol*. 2019;30:1746–1755. https://doi.org/10.1681/ASN.2019010008
25. Inker LA, Heerspink HJL, Tighiouart H, et al. GFR slope as a surrogate end point for kidney disease progression in clinical trials: a meta-analysis of treatment effects of randomized controlled trials. *J Am Soc Nephrol*. 2019;30:1735–1745. https://doi.org/10.1681/ASN.2019010007
26. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the treatment of preserved cardiac function heart failure with an aldosterone antagonist (TOPCAT) trial. *Circulation*. 2015;131:34–42. https://doi.org/10.1161/CIRCULATIONAHA.114.013255
27. de Denus S, O'Meara E, Desai AS, et al. Spironolactone metabolites in TOPCAT -new insights into regional variation. *N Engl J Med*. 2017;376:1690–1692. https://doi.org/10.1056/NEJMc1612601
28. Parasuraman S, Walker S, Loudon BL, et al. Assessment of pulmonary artery pressure by echocardiography-a comprehensive review. *Int J Cardiol Heart Vasc*. 2016;12:45–51. https://doi.org/10.1016/j.ijcha.2016.05.011
29. Lam CSP, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. *J Am Coll Cardiol*. 2009;53:1119–1126. https://doi.org/10.1016/J.JACC.2008.11.051
30. Navaneethan SD, Roy J, Tao K, et al. Prevalence, predictors, and outcomes of pulmonary hypertension in CKD. *J Am Soc Nephrol*. 2016;27:877–886. https://doi.org/10.1681/ASN.2014111111
31. Thenappan T, Shah SJ, Gomberg-Maitland M, et al. Clinical characteristics of pulmonary hypertension in patients with heart failure and preserved ejection fraction. *Circ Heart Fail*. 2011;4:257–265. https://doi.org/10.1161/CIRCHEARTFAILURE.110.958801
32. Kjaergaard J, Akkan D, Iversen KK, et al. Prognostic importance of pulmonary hypertension in patients with heart failure. *Am J Cardiol*. 2007;99:1146–1150. https://doi.org/10.1016/J.AMJCARD.2006.11.052
33. Rosenkranz S, Howard LS, Gomberg-Maitland M, Hoeper MM. Systemic consequences of pulmonary hypertension and right-sided heart failure. *Circulation*. 2020;141:678–693. https://doi.org/10.1161/CIRCULATIONAHA.116.022362
34. Ross EA. Congestive renal failure: the pathophysiology and treatment of renal venous hypertension. *J Card Fail*. 2012;18:930–938. https://doi.org/10.1016/J.CARDFAIL.2012.10.010
35. Fiksen-Olsen MJ, Strick DM, Hawley H, Romero JC. Renal effects of angiotensin II inhibition during increases in renal venous pressure. *Hypertension*. 1992;19:II137–II141. https://doi.org/10.1161/01.HYP.19.2_SUPPL.II137
36. Doty JM, Saggi BH, Sugerman HJ, et al. Effect of increased renal venous pressure on renal function. *J Trauma*. 1999;47:1000–1003. https://doi.org/10.1097/00005373-199912000-00002
37. Shah SJ, Thenappan T, Rich S, Tian L, Archer SL, Gomberg-Maitland M. Association of serum creatinine with abnormal hemodynamics and mortality in pulmonary arterial hypertension. *Circulation*. 2008;117:2475–2483. https://doi.org/10.1161/CIRCULATIONAHA.107.719500
38. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol*. 2009;53:589–596. https://doi.org/10.1016/j.jacc.2008.05.068
39. Schwartzenberg S, Redfield MM, From AM, Sorajja P, Nishimura RA, Borlaug BA. Effects of vasodilation in heart failure with preserved or reduced ejection fraction implications of distinct pathophysiologies on response to therapy. *J Am Coll Cardiol*. 2012;59:442–451. https://doi.org/10.1016/J.JACC.2011.09.062
40. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation*. 2003;107:714–720. https://doi.org/10.1161/01.CIR.0000048123.22359.A0
41. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. *Lancet*. 2012;380:756–766. https://doi.org/10.1016/S0140-6736(11)61454-2
42. Damman K, Voors AA, Navis G, van Veldhuisen DJ, Hillege HL. The cardiorenal syndrome in heart failure. *Prog Cardiovasc Dis*. 2011;54:144–153. https://doi.org/10.1016/J.PCAD.2011.01.003
43. Adamson PB, Abraham WT, Bourge RC, et al. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. *Circ Hear Fail*. 2014;7:935–944. https://doi.org/10.1161/CIRCHEARTFAILURE.113.001229
44. Janda S, Shahidi N, Gin K, Swiston J. Diagnostic accuracy of echocardiography for pulmonary hypertension: a systematic review and meta-analysis. *Heart*. 2011;97:612–622. https://doi.org/10.1136/HRT.2010.212084
45. Parent F, Bachir D, Inamo J, et al. A hemodynamic study of pulmonary hypertension in sickle cell disease. *N Engl J Med*. 2011;365:44–53. https://doi.org/10.1056/NEJMOA1005565
46. Zile MR, Gottdiener JS, Hetzel SJ, et al. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation*. 2011;124:2491–2501. https://doi.org/10.1161/CIRCULATIONAHA.110.011031
47. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet*. 2012;380:1387–1395. https://doi.org/10.1016/S0140-6736(12)61227-6
48. Redfield MM, Chen HH, Borlaug BA, et al. Effect of Phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: A randomized clinical trial. *JAMA*. 2013;309:1268–1277. https://doi.org/10.1001/JAMA.2013.2024