

Cardiac Structure and Function and Quality of Life associations in HFpEF: an analysis from TOPCAT-Americas

João Pedro Ferreira, MD, PhD^{1,2}; Amil M. Shah, MD³; Brian L. Claggett, PhD³;
Bertram Pitt, MD⁴; Eldrin F. Lewis, MD⁵; Scott D. Solomon, MD³; Faiez Zannad, MD,
PhD¹

¹ Université de Lorraine, Inserm, Centre d'Investigations Cliniques Plurithématique 1433, and Inserm U1116, CHRU, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France.

² Cardiovascular Research and Development Center, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, Porto, Portugal.

³ Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA.

⁴ Department of Medicine, University of Michigan School of Medicine, Ann Arbor, Michigan, USA.

⁵ Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford University, Palo Alto, California, USA.

Contact to:

Dr João Pedro Ferreira

Centre d'Investigation Clinique 1433 module Plurithématique, CHRU Nancy -
Hopitaux de Brabois, Institut Lorrain du Coeur et des Vaisseaux Louis Mathieu
4 rue du Morvan, 54500 Vandoeuvre les Nancy

Tel : +33 (0) 3 83 15 73 15

Fax : +33 (0) 3 83 15 73 24

Mail: j.ferreira@chru-nancy.fr

Abstract

Background: Patients with heart failure with preserved ejection fraction (HFpEF) have poor health-related quality of life (HR-QoL). However, the relationship between HR-QoL measures and the alterations of cardiac structure and function that are present in patients with HFpEF remains unknown.

Aims: To study the associations between HR-QoL and echocardiographic parameters in HFpEF.

Methods: Regression modelling in patients from TOPCAT-Americas who had both HR-QoL questionnaires and a baseline echocardiogram.

Results: A total of 631 patients (36% of the TOPCAT-Americas population) had both echocardiographic and HR-QoL at baseline. KCCQ-23 Overall Summary Score (OSS; 0-100 points) was negatively (higher echocardiographic values-poorer/lower HR-QoL scores) associated with left ventricular end-diastolic diameter (LVEDD: $\beta=-3.56$ [-7.00 to -0.13] points-per-1cm, $P=0.042$), interventricular septum thickness ($\beta=-1.31$ [-2.19 to -0.42] points-per-1mm, $P=0.004$), posterior wall thickness ($\beta=-1.57$ [-2.52 to -0.63] points-per-1mm, $P=0.001$) and left atrial width ($\beta=-3.27$ [-6.39 to -0.15], $P=0.040$) points-per-1cm, and positively (higher echocardiographic values-better/higher HR-QoL scores) associated with left ventricular end-diastolic volume index (LVEDVi: $\beta=0.23$ [0.09 to 0.37] points-per-1ml/m², $P=0.002$) and left ventricular end-systolic volume index (LVESVi: $\beta=0.41$ [0.18 to 0.63] points-per-1ml/m², $P<0.001$). Body mass index (BMI: $\beta=-0.74$ [-1.02 to -0.47] points-per-1Kg/m², $P<0.001$), diabetes ($\beta=-6.01$ [-10.05 to -1.97], $P=0.004$), and asthma ($\beta=-6.78$ [-13.52 to -0.04], $P=0.049$) were negatively associated with OSS. A similar pattern of associations was observed for KCCQ-23 Clinical Summary Score, EQ5D-VAS and NYHA class.

Conclusion: In patients with HFpEF, HR-QoL measures were associated with cardiac structure and function alterations. Extra-cardiac factors were also associated with HR-QoL, which may influence HR-QoL results when testing cardiovascular drugs.

Key-words: health related quality of life; echocardiography; heart failure with preserved ejection fraction; spironolactone.

Introduction

Patients with heart failure and a preserved ejection fraction (HFpEF) have a poor quality of life limiting their daily activities and social interactions.¹ Health-related quality of life (HR-QoL) measures correlate well with the clinical status of the patient and have prognostic value.² The Kansas City Cardiomyopathy Questionnaire 23 (KCCQ-23) has been used as the primary tool for evaluating HR-QoL in heart failure (HF).³ In the Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function (TOPCAT) trial, lower KCCQ-23 scores were associated with poor outcomes and spironolactone improved KCCQ-23 by 1 to 2 points on average up to month 36 of follow-up.^{2,4} In TOPCAT-Americas, spironolactone improved cardiac structure and function, and reduced HF hospitalizations.⁵⁻⁹

Despite the modest improvement of HR-QoL with spironolactone treatment and the beneficial effect of spironolactone to improve cardiac structure and function and reduce HF hospitalizations, it is not well-established to which extent HR-QoL measures are related to alterations of cardiac structure and function. Furthermore, whether “extra-cardiac” factors (that may not be impacted by HF drugs) may also be associated with HR-QoL is worth exploring.¹

In the present analysis we aim to study the associations between HR-QoL scores, echocardiographic and “extra-cardiac” parameters in HFpEF patients enrolled in TOPCAT-Americas.

Methods

Patient population

TOPCAT was a multinational, double-blind, randomized, placebo-controlled, parallel-group study that investigated the effects of spironolactone versus placebo on clinical outcomes in patients with HFpEF. The rationale and design of the study have been previously published.¹⁰ In short, the trial included 3445 patients >50 years of age with symptomatic HF and preserved ejection fraction (defined as a LVEF \geq 45%), who were followed for a median of 3 years. Eligible patients had a systolic blood pressure <140 mmHg, serum potassium <5.0 mmol/L, and either a prior HF hospitalization within 12 months or elevated natriuretic peptide levels (B-type natriuretic peptide \geq 100 pg/mL or N-terminal pro-B-type natriuretic peptide \geq 360 pg/mL). Key exclusion criteria were severe renal dysfunction (defined as estimated glomerular function rate <30 ml/ min/1.73 m² or serum creatinine \geq 2.4 mg/dl), severe systemic illness with life expectancy of <3 years from randomization and use of an aldosterone antagonist or potassium sparing diuretic agent within 14 days before randomization.

Due to previously reported differences in patient demographics, event rates, adherence to study medication, responses to treatment, and outcomes among TOPCAT subjects enrolled in Russia and the Republic of Georgia, we restricted our analyses to the subset of TOPCAT subjects enrolled in the Americas (United States, Canada, Argentina, Brazil; N =1767).^{5,6,11}

All patients provided informed consent. The protocol was approved by the Institutional Review Board at each of the participating centers prior to enrollment of the first patient. The study was overseen by the Institutional Review Board.

Quality of life assessment

The primary HR-QoL outcome measure was the KCCQ-23. The KCCQ is a HF-specific 23-item self-administered questionnaire developed to evaluate HF patients' HR-QoL, symptoms, and function. Domains include physical limitation, symptoms (frequency, severity, and change over time), quality of life, social limitations, and self-efficacy. Each response is given an ordinal value, and scale scores are transformed into a 0 to 100 range, with higher scores indicating better HR-QoL. KCCQ has been validated in HF populations, including in HFpEF, and is responsive to important changes in health state.¹² The KCCQ-23 Overall Summary Score (OSS) is defined as the mean of the Physical Limitation, Total Symptom, Quality of Life and Social Limitation Scores. The Clinical Summary Score (CSS) is defined as the mean of the Physical Limitation and Total Symptom Scores.

The visual analogic scale (VAS) component of the EQ5D was used; VAS is a vertical scale from 0 to 100, with 0 representing the worst possible HR-QoL and 100 representing the best possible HR-QoL.

The NYHA class is assigned by the clinicians after inquiring patients about their symptoms and has four classes in which class I represents no or very mild symptoms and IV the worst possible symptoms at rest.

Echocardiographic assessment

Echocardiograms were sent in digital or analog format to the echo core laboratory at the Brigham and Women's Hospital. Echocardiograms from videotape were digitized and analyses were performed on an offline analysis workstation. Quantitative measures on all study Echocardiograms were performed by dedicated analysts at the core laboratory, blinded to clinical information and randomized treatment assignment. A detailed description of the echocardiographic parameters has been

previously published.¹³ In short, LV endocardial borders were manually traced at end-diastole and end-systole in the apical 4- and 2-chamber views and LV volumes derived according to the modified biplane Simpson's rule. In cases where the Simpson's method could not be used due to missing or poor-quality apical views, LVEF was calculated using the Teicholz method (n =14). LV mass was calculated by the American Society of Echocardiography (ASE) recommended formula for estimation of LV mass from LV linear dimensions and indexed to body surface area (LVMI).¹⁴ LA volume was assessed by the biplane area-length method from apical 2- and 4-chamber views at end-systole from the frame preceding mitral valve opening and was indexed to body surface area (LAVi). Peak early diastolic tissue velocity (e') was measured from the septal and lateral aspects of the mitral annulus. Mitral inflow velocity was assessed by pulsed wave Doppler from the apical 4-chamber view, by positioning the sample volume at the tip of the mitral leaflets. The deceleration time of the E wave was measured as the interval from the peak E wave to its extrapolation to the baseline. E/e' ratio was calculated as E wave divided by e'. Right ventricular (RV) function, expressed as the RV fractional area change (RVFAC), was assessed as the percent change in cavity area from end-diastole to end-systole.¹⁵ Peak tricuspid regurgitation (TR) velocity was measured and peak RV-to-RA systolic gradient was calculated as $4 \cdot (\text{peak TR velocity})^2$. Pulmonary vascular resistance (PVR) was estimated as $0.1618 + (10.006 \cdot [\text{peak TR velocity} / \text{right ventricular outflow tract time-velocity integral}])$.¹⁶

Statistical analysis

For descriptive statistics, TOPCAT-Americas patients were compared between those with available HR-QoL measures and echocardiogram and those without KCCQ-23 and echocardiogram available. Patients' characteristics are presented as median

(percentile₂₅₋₇₅), or numbers and percentages. To study the associations between the HR-QoL measures and echocardiographic parameters, linear regression models were used when the outcome variable of interest was continuous (e.g., total symptom score, overall summary score, clinical summary score, and VAS) and ordered logistic regression models were used when the outcome variable of interest was ordinal (e.g., individual questions of KCCQ-23 and NYHA class). All models were adjusted for age and sex. To explore the association of “cardiac” and “extra-cardiac factors” with the total symptom score, overall summary score, clinical summary score, and VAS, stepwise forward linear regression models were used including all variables from Table 1 plus echocardiographic parameters. Spearman correlation was calculated between OSS and echocardiographic variables of interest. Among patients in whom an echocardiogram was available at 12-18 months, the changes in echocardiographic parameters by treatment (spironolactone vs. placebo) were calculated by analysis of covariance (ANCOVA) and the changes in echocardiographic parameters were correlated with changes in KCCQ-23. Two-tailed p values <0.05 were considered statistically significant. No correction for test multiplicity was performed given the exploratory nature of this work. Statistical analyses were performed using STATA® Statistical Software version 17.0 (STATA Corp, College Station, Texas).

Results

Characteristics of the patients at baseline

A total of 631 patients (36% of the TOPCAT-Americas population) had both echocardiographic and HR-QoL measures at baseline. Patients with both echocardiographic and HR-QoL measures had similar characteristics to those

without both measures, except that those with both measures were less frequently White (75 vs. 80%), had slightly lower hemoglobin levels (12.6 vs. 12.9 g/dL), and used beta-blockers more frequently (81 vs. 76%). *Table 1*. The median age was 72 years and nearly 50% were women.

The echocardiographic characteristics are described in the *Supplemental Table 1* and the HR-QoL measures including the KCCQ-23 components in the *Supplemental Table 2*.

Association of health-related quality of life with echocardiographic parameters

Adjusting for sex and age, and significantly at $P < 0.05$; the KCCQ-23 OSS was positively (higher echocardiographic values - better/higher scores) associated with left ventricular end-diastolic volume indexed to body surface area (LVEDVi: $\beta = 0.23$ [0.09 to 0.37] points per each 1ml/m² higher, $P = 0.002$) and left ventricular end-systolic volume indexed to body surface area (LVESVi: $\beta = 0.41$ [0.18 to 0.63] points per each 1ml/m² higher, $P < 0.001$), and negatively (higher echocardiographic values - poorer/lower scores) associated with left ventricular end-diastolic diameter (LVEDD: $\beta = -3.56$ [-7.00 to -0.13] points per each 1cm higher, $P = 0.042$), interventricular septum thickness ($\beta = -1.31$ [-2.19 to -0.42] points per each 1mm higher, $P = 0.004$), posterior wall thickness ($\beta = -1.57$ [-2.52 to -0.63] points per each 1mm higher, $P = 0.001$) and left atrial width ($\beta = -3.27$ [-6.39 to -0.15] points per each 1cm larger, $P = 0.040$). *Table 2*. A similar pattern was observed for the KCCQ-23 CSS, with the addition of LVEF ($\beta = -0.26$ [-0.5 to -0.03] points per each 1% higher, $P = 0.026$) and pulmonary vascular resistance (PVR: -2.73 [-5.31 to -0.15] points per each Wood unit increase, $P = 0.038$). The EQ5D-VAS and NYHA displayed a similar association pattern to that of OSS and CSS. Additionally, global longitudinal strain (GLS) and septal TDI e' were also associated with NYHA. *Table 2*. For a correct

interpretation of the coefficients, it should be noted that NYHA has an opposite direction to that of KCCQ-23 and VAS (higher NYHA = worse vs higher KCCQ-23 = better).

The associations of the echocardiographic parameters and each individual KCCQ-23 question is displayed in the *Supplemental Table 3*, with a similar pattern of associations to those above described for the composite scores.

The correlation between the OSS and LVEF, interventricular septum thickness, left atrial width, and GLS in both men and women is depicted in *Figure 1*. The correlations were overall weak ($Rho < 0.3$ for all), but women had a stronger correlation with interventricular septum thickness ($Rho = -0.20$, $P = 0.001$) compared with men ($Rho = -0.07$, $P = 0.20$).

Cardiac and extra-cardiac factors associated with health-related quality of life

In multivariable stepwise models, OSS was independently associated with the “extra-cardiac factors” body mass index (BMI: $\beta = -0.74$ [-1.02 to -0.47] points per each 1Kg/m² higher, $P < 0.001$), diabetes ($\beta = -6.01$ [-10.05 to -1.97] points if diabetes, $P = 0.004$), and asthma ($\beta = -6.78$ [-13.52 to -0.04] points if asthma, $P = 0.049$), plus the “cardiac factors” heart rate ($\beta = -0.20$ [-0.37 to -0.02] points per each 1bpm higher, $P = 0.025$) and LVEDVi ($\beta = 0.19$ [0.05 to 0.33] points per each 1ml/m² higher, $P = 0.007$). A similar pattern of associations was found for CSS with LVEF ($\beta = -0.41$ [-0.66 to -0.17] points per each 1% higher, $P = 0.001$) instead of LVEDVi as “cardiac factor”, and non-White race ($\beta = -5.30$ [-9.94 to -0.66] points if White, $P = 0.025$) instead of asthma as “non-cardiac factor”. *Table 3*. The VAS scale was negatively associated with BMI, LVEF, and previous myocardial infarction (MI), and NYHA

association was associated with older age, diabetes, previous HF hospitalization, BMI, and atrial fibrillation. *Table 3.*

Correlation of changes in echocardiographic parameters with changes in health-related quality of life

In patients who had a repeated echocardiogram at 12 or 18 months and HR-QoL measures (n =134), spironolactone improved E/A ratio ($\beta = -0.24$ [-0.46 to -0.01] unit, $P =0.043$), lateral E/e' ($\beta = -2.36$ [-3.96 to -0.75] unit, $P =0.005$), and tended to improve LVEF ($\beta =2.02$ [-0.09 to 4.13] %, $P =0.061$) and LAVi ($\beta = -2.45$ [-5.32 to 0.42] ml/m², $P =0.094$). Among these 134 patients, spironolactone improved KCCQ-23 OSS ($\beta =2.29$ [0.12 to 4.47] points, $P =0.039$) but not the KCCQ-23 CSS ($\beta =1.47$ [-0.67 to 3.62] points, $P =0.18$).

The changes in OSS were not correlated with the echocardiographic changes ($Rho <0.10$, $P >0.05$ for all).

Discussion

The present study shows that in patients with HFpEF baseline HR-QoL measures are associated with echocardiographic parameters reflecting cardiac structure and function; moreover, “extra-cardiac” factors (e.g., obesity, race, diabetes, and pulmonary diseases) may influence HR-QoL. Therefore, in HFpEF patients with many co-morbid conditions (as often occurs), HR-QoL may reflect “extra-cardiac” co-morbidities and be less impacted by treatments that primarily improve cardiac function. These findings should be taken in consideration when using HR-QoL measures as outcomes in HFpEF trials.

The association of cardiac alterations assessed by echocardiography with HR-QoL was consistent and followed a coherent pattern across various HR-QoL measures.

Specifically, KCCQ-23 OSS and CSS, EQ5D-VAS, and NYHA class were negatively associated with alterations in the heart reflecting hypertrophy (higher septum and posterior wall thickness), ejection fraction (higher LVEF), size of the left ventricle and left atria (greater LVEDD, LVESD and left atrial width), and pulmonary vascular resistances (higher PVR). Worse NYHA class was also associated with measures of diastolic dysfunction (higher E/A ratio and septal TDI e') and left ventricular systolic impairment as assessed by strain analysis (lower LV global longitudinal strain). On the other hand, KCCQ-23 OSS and CSS, EQ5D-VAS, and NYHA class were positively associated with alterations in the heart reflecting volumes of the left ventricle (LVEDVi and LVESVi).

The negative associations between HR-QoL and myocardial hypertrophy/LV wall thickness, suggests that concentric remodelling and hypertrophy play an important role in the symptomatology and progression of HFpEF.¹⁷ Enhanced neurohumoral activation, increased mechanical load, and the release of cytokines associated with chronic kidney disease, diabetes, respiratory diseases and other comorbid conditions induce micro- and macro vascular dysfunction and alterations in the extracellular matrix leading to interstitial fibrosis and heart stiffness causing hypertrophy of the heart.^{18,19}

Left atrial enlargement and adverse remodelling of the atria contribute to the progression of HFpEF, and most patients with symptomatic HFpEF present dilation of the left atria, which is consistent with the associations here described with worse HR-QoL among patients with larger left atria.²⁰⁻²² In patients at risk for developing HF enrolled in the Heart Omics in Ageing (HOMAGE) trial, spironolactone reduced the size and volume of the left atria, blood pressure and circulating peptides related to collagen synthesis.²³⁻²⁵

Increased PVR in patients with HF may be secondary to “left heart” dysfunction; however, a dedicated diagnostic workflow for increased PVR was not available in TOPCAT.²⁶ Notwithstanding, in patients with chronic HF the resulting pulmonary hypertension directly affects HR-QoL, exercise capacity, morbidity, and mortality.²⁷

Measures reflecting diastolic function and LV filling pressure (e.g., septal TDI e') and systolic function independently of ejection fraction (i.e., LV global longitudinal strain) also influence HR-QoL and prognosis in HFpEF.^{28,29} In TOPCAT, patients with an impaired LV global longitudinal strain had a worse prognosis (i.e., higher rates of cardiovascular death, HF hospitalization and aborted cardiac arrest) than patients without systolic impairment as assessed by “strain” analysis.⁸ Furthermore, spironolactone treatment was associated with a trend towards LV global longitudinal strain improvement in TOPCAT-Americas.⁸

Volumes of the left ventricle (i.e., LVEDVi and LVESVi) were positively associated with better HR-QoL. In HFpEF, LV volumes correlate poorly with LV size and structure (e.g., in TOPCAT the correlation between volumes and diameters of the LV was <0.5), and may reflect a better cardiac function with less cardiac hypertrophy and a more efficient relaxation and contraction of the LV.^{13,30,31} This is an important distinction between HFpEF and HFrEF, because in HFpEF the LVEDV is appropriate for the stroke volume, whereas in HFrEF the LVEDV is enlarged relative to stroke volume (because the LV is dilated).³² Consistently, in TOPCAT, a higher LVEF was associated with worse HR-QoL. Heart hypertrophy, frequently found in HFpEF, leads to small heart volumes and a high LVEF, which explains the associations between better HR-QoL with higher heart volumes and worse HR-QoL with higher LVEF.^{31,33}

Several “extra-cardiac” factors, such as older age, higher body mass index, diabetes, and asthma had a negative association with HR-QoL. Other studies have found that HR-QoL was poorer among obese and diabetic patients and was not influenced by indices of resting echocardiography.¹ These “extra-cardiac” factors are not impacted by spironolactone or other “cardiovascular” drugs (e.g., ACEi/ARBs, beta-blockers, vasodilators or sacubitril/valsartan); thus, the contribution of these extra-cardiac factors to HR-QoL should be taken into account when using “patient-centered” outcomes in HFpEF clinical trials as they may only partially reflect improvements of cardiac function, which may lead to small changes in HR-QoL (i.e., lower than the usually used 5-point threshold). However, these small changes may have clinical importance.³⁴ Other studies have shown that patients with higher relative contribution of cardiac comorbidities may benefit more from cardiac disease-modifying medications compared with patients with higher relative contribution of extra-cardiac comorbidities.^{35,36}

The changes in echocardiographic structure and function were not correlated with the changes in HR-QoL, these findings may be limited by the small sample and effect size magnitude; still, they support the dissociation between cardiac structure and function and HR-QoL, the latter being influenced by many other “extra-cardiac” factors.

Limitations

Several limitations should be acknowledged in our work. This is a post-hoc analysis of a randomized trial with the limitations inherent to observational studies, particularly we report associations and causation cannot be inferred. We have performed multiple analysis without correction for multiple testing, therefore some of the finding might have occurred by chance and these results should be regarded as exploratory.

Nonetheless, a consistent pattern of observations was seen. The findings here observed may be specific of the elderly HFpEF population enrolled in TOPCAT-Americas, and despite similar results have been described in other cohorts, further replication is required. Furthermore, the positive association between LV volumes and HR-QoL may be a spurious finding or a result specific of this cohort; beyond further replication, expanding this analysis to patients with reduced LVEF would allow to better understand the interplay between LV diameters, volumes and HR-QoL.

Conclusions

In patients with HFpEF enrolled in TOPCAT-Americas, HR-QoL measures were associated with alterations in cardiac structure and function. Extra-cardiac factors also contributed to HR-QoL, which may influence HR-QoL results when testing cardiovascular drugs.

Funding

The TOPCAT study was supported by a contract from the National Heart, Lung, and Blood Institute, National Institutes of Health (HHSN268200425207C).

The content of this manuscript is solely the responsibility of the authors and does not necessarily reflect the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

Disclosures

The authors have no relevant conflicts of interest to report regarding the content of this study.

References

1. Reddy YNV, Rikhi A, Obokata M, et al. Quality of life in heart failure with preserved ejection fraction: importance of obesity, functional capacity, and physical inactivity. *Eur J Heart Fail*. Mar 9 2020;doi:10.1002/ejhf.1788
2. Pokharel Y, Khariton Y, Tang Y, et al. Association of Serial Kansas City Cardiomyopathy Questionnaire Assessments With Death and Hospitalization in Patients With Heart Failure With Preserved and Reduced Ejection Fraction: A Secondary Analysis of 2 Randomized Clinical Trials. *JAMA Cardiol*. Dec 1 2017;2(12):1315-1321. doi:10.1001/jamacardio.2017.3983
3. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol*. Apr 2000;35(5):1245-55.
4. Lewis EF, Kim HY, Claggett B, et al. Impact of Spironolactone on Longitudinal Changes in Health-Related Quality of Life in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial. *Circ Heart Fail*. Mar 2016;9(3)doi:10.1161/circheartfailure.114.001937
5. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. Apr 10 2014;370(15):1383-92. doi:10.1056/NEJMoa1313731
6. 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*. Jan 6 2015;131(1):34-42. doi:10.1161/circulationaha.114.013255
7. Shah AM, Claggett B, Sweitzer NK, et al. Cardiac structure and function and prognosis in heart failure with preserved ejection fraction: findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial. *Circ Heart Fail*. Sep 2014;7(5):740-51. doi:10.1161/circheartfailure.114.001583
8. Shah AM, Claggett B, Sweitzer NK, et al. Prognostic Importance of Impaired Systolic Function in Heart Failure With Preserved Ejection Fraction and the Impact of Spironolactone. *Circulation*. Aug 4 2015;132(5):402-14. doi:10.1161/circulationaha.115.015884
9. Solomon SD, Claggett B, Lewis EF, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J*. Feb 1 2016;37(5):455-62. doi:10.1093/eurheartj/ehv464
10. 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*. Dec 2011;162(6):966-972.e10. doi:10.1016/j.ahj.2011.09.007
11. de Denus S, O'Meara E, Desai AS, et al. Spironolactone Metabolites in TOPCAT - New Insights into Regional Variation. *N Engl J Med*. Apr 27 2017;376(17):1690-1692. doi:10.1056/NEJMc1612601
12. Joseph SM, Novak E, Arnold SV, et al. Comparable performance of the Kansas City Cardiomyopathy Questionnaire in patients with heart failure with preserved and reduced ejection fraction. *Circ Heart Fail*. Nov 2013;6(6):1139-46. doi:10.1161/circheartfailure.113.000359

13. Shah AM, Shah SJ, Anand IS, 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 trial. *Circ Heart Fail*. Jan 2014;7(1):104-15. doi:10.1161/circheartfailure.113.000887
14. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. Dec 2005;18(12):1440-63. doi:10.1016/j.echo.2005.10.005
15. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. Jul 2010;23(7):685-713; quiz 786-8. doi:10.1016/j.echo.2010.05.010
16. Abbas AE, Fortuin FD, Schiller NB, Appleton CP, Moreno CA, Lester SJ. A simple method for noninvasive estimation of pulmonary vascular resistance. *J Am Coll Cardiol*. Mar 19 2003;41(6):1021-7. doi:10.1016/s0735-1097(02)02973-x
17. Lam CS, Grewal J, Borlaug BA, et al. Size, shape, and stamina: the impact of left ventricular geometry on exercise capacity. *Hypertension*. May 2010;55(5):1143-9. doi:10.1161/hypertensionaha.109.146845
18. Heinzl 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)*. Nov 15 2015;119(10):1233-42. doi:10.1152/jappphysiol.00374.2015
19. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol*. Jul 23 2013;62(4):263-71. doi:10.1016/j.jacc.2013.02.092
20. 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*. Dec 6 2011;124(23):2491-501. doi:10.1161/circulationaha.110.011031
21. Lam CS, 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*. Mar 31 2009;53(13):1119-26. doi:10.1016/j.jacc.2008.11.051
22. Rossi A, Gheorghide M, Triposkiadis F, Solomon SD, Pieske B, Butler J. Left atrium in heart failure with preserved ejection fraction: structure, function, and significance. *Circ Heart Fail*. Nov 2014;7(6):1042-9. doi:10.1161/circheartfailure.114.001276
23. Cleland JGF, Ferreira JP, Mariottoni B, et al. The effect of spironolactone on cardiovascular function and markers of fibrosis in people at increased risk of developing heart failure: the heart 'OMics' in AGEing (HOMAGE) randomized clinical trial. *Eur Heart J*. Nov 20 2020;doi:10.1093/eurheartj/ehaa758
24. Ferreira JP, Verdonschot J, Wang P, et al. Proteomic and Mechanistic Analysis of Spironolactone in Patients at Risk for HF. *JACC Heart Fail*. Jan 28 2021;doi:10.1016/j.jchf.2020.11.010

25. Ferreira JP, Collier T, Clark AL, et al. Spironolactone effect on the blood pressure of patients at risk of developing heart failure: an analysis from the HOMAGE trial. *Eur Heart J Cardiovasc Pharmacother.* Apr 2 2021;doi:10.1093/ehjcvp/pvab031
26. Rich JD, Rich S. Clinical diagnosis of pulmonary hypertension. *Circulation.* Nov 11 2014;130(20):1820-30. doi:10.1161/circulationaha.114.006971
27. Moraes DL, Colucci WS, Givertz MM. Secondary pulmonary hypertension in chronic heart failure: the role of the endothelium in pathophysiology and management. *Circulation.* Oct 3 2000;102(14):1718-23. doi:10.1161/01.cir.102.14.1718
28. Tan YT, Wenzelburger F, Lee E, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. *J Am Coll Cardiol.* Jun 30 2009;54(1):36-46. doi:10.1016/j.jacc.2009.03.037
29. Opdahl A, Remme EW, Helle-Valle T, et al. Determinants of left ventricular early-diastolic lengthening velocity: independent contributions from left ventricular relaxation, restoring forces, and lengthening load. *Circulation.* May 19 2009;119(19):2578-86. doi:10.1161/circulationaha.108.791681
30. Kerkhof PL. Characterizing heart failure in the ventricular volume domain. *Clin Med Insights Cardiol.* 2015;9(Suppl 1):11-31. doi:10.4137/cmc.s18744
31. Yeboah J, Bluemke DA, Hundley WG, Rodriguez CJ, Lima JA, Herrington DM. Left ventricular dilation and incident congestive heart failure in asymptomatic adults without cardiovascular disease: multi-ethnic study of atherosclerosis (MESA). *J Card Fail.* Dec 2014;20(12):905-11. doi:10.1016/j.cardfail.2014.09.002
32. Iwano H, Little WC. Heart failure: what does ejection fraction have to do with it? *J Cardiol.* Jul 2013;62(1):1-3. doi:10.1016/j.jjcc.2013.02.017
33. Chen X, Xin Y, Hu W, Zhao Y, Zhang Z, Zhou Y. Quality of life and outcomes in heart failure patients with ejection fractions in different ranges. *PLoS One.* 2019;14(6):e0218983. doi:10.1371/journal.pone.0218983
34. Ferreira JP. Health-related quality of life scores: ending the minimum 5-point difference as the clinically meaningful threshold. *Eur J Heart Fail.* Jun 2020;22(6):1006-1008. doi:10.1002/ejhf.1822
35. Wolsk E, Claggett B, Køber L, et al. Contribution of cardiac and extra-cardiac disease burden to risk of cardiovascular outcomes varies by ejection fraction in heart failure. *Eur J Heart Fail.* Mar 2018;20(3):504-510. doi:10.1002/ejhf.1073
36. Rohde LE, Claggett BL, Wolsk E, et al. Cardiac and Noncardiac Disease Burden and Treatment Effect of Sacubitril/Valsartan: Insights From a Combined PARAGON-HF and PARADIGM-HF Analysis. *Circ Heart Fail.* Mar 2021;14(3):e008052. doi:10.1161/circheartfailure.120.008052

Table 1. Baseline characteristics of patients with and without echocardiogram and health-related quality of life measures

Characteristic	No Echo. and QoL	Echo. and QoL	P-value
N.	1136	631	
Age (years)	72.0 (64.0, 79.0)	72.0 (63.0, 79.0)	0.45
Women	578 (50.9%)	304 (48.2%)	0.28
White race	909 (80.0%)	475 (75.3%)	0.029
Body mass index (kg/m ²)	32.9 (27.7, 38.6)	32.7 (28.4, 38.1)	1.00
NYHA III	392 (34.6%)	228 (36.1%)	0.51
Systolic blood pressure (mmHg)	129.0 (118.0, 139.0)	128.0 (117.0, 138.0)	0.52
Heart rate (bpm)	68.0 (61.0, 76.0)	68.0 (61.0, 76.0)	0.69
Ejection fraction (%)	59.0 (53.0, 64.0)	58.0 (52.0, 63.0)	0.33
Hypertension	1014 (89.3%)	574 (91.1%)	0.24
Diabetes	491 (43.3%)	297 (47.1%)	0.12
Atrial Fibrillation / Flutter	283 (25.3%)	163 (26.1%)	0.71
Previous MI	371 (32.7%)	196 (31.1%)	0.50
Previous stroke	104 (9.2%)	46 (7.3%)	0.17
Previous HF hospitalisation	664 (58.5%)	376 (59.7%)	0.63
COPD	185 (16.3%)	106 (16.8%)	0.78
eGFR (ml/min/1.73m ²)	61.7 (49.6, 77.0)	59.8 (48.1, 76.0)	0.11
Hemoglobin (g/dL)	12.9 (11.7, 14.1)	12.6 (11.6, 13.9)	0.005
Potassium (mmol/L)	4.2 (3.9, 4.5)	4.2 (3.9, 4.5)	0.12
ACEi/ARBs	889 (78.3%)	496 (78.6%)	0.89
Beta-blockers	867 (76.4%)	512 (81.1%)	0.021
Diuretics	1001 (88.2%)	562 (89.1%)	0.58

Legend: NYHA, New York Heart Association; MI, myocardial infarction; HF, heart failure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ACEi/ARBs, angiotensin converting enzyme / angiotensin receptor blockers.

Table 2. Association between health-related quality of life and echocardiographic parameters

QoL measure	N	Beta coef. (95%CI)	P-value
Overall Summary Score (0-100 points)			
LVEDVi (ml/m ²)	574	0.23 (0.09 to 0.37)	0.002
LVESVi (ml/m ²)	574	0.41 (0.18 to 0.63)	<0.001
LVEDD (cm)	624	-3.56 (-7.0 to -0.13)	0.042
Septum thickness (mm)	624	-1.31 (-2.19 to -0.42)	0.004
Posterior wall thickness (mm)	623	-1.57 (-2.52 to -0.63)	0.001
Left atrial width (cm)	624	-3.27 (-6.39 to -0.15)	0.04
Clinical Summary Score (0-100 points)			
LVEDVi (ml/m ²)	574	0.20 (0.06 to 0.33)	0.005
LVESVi (ml/m ²)	574	0.39 (0.17 to 0.62)	0.001
Septum thickness (mm)	624	-1.31 (-2.18 to -0.45)	0.003
Posterior wall thickness (mm)	623	-1.68 (-2.61 to -0.76)	<0.001
LVEF (%)	631	-0.26 (-0.5 to -0.03)	0.026
PVR (Woods units)	276	-2.73 (-5.31 to -0.15)	0.038
VAS scale (0-10 points)			
LVEDVi (ml/m ²)	572	0.13 (0.02 to 0.25)	0.027
LVESVi (ml/m ²)	572	0.28 (0.09 to 0.47)	0.005
LVEDD (cm)	623	-3.26 (-6.17 to -0.35)	0.028
Septum thickness (mm)	623	-0.88 (-1.63 to -0.13)	0.021
Posterior wall thickness (mm)	622	-1.35 (-2.16 to -0.55)	0.001
LVEF (%)	630	-0.22 (-0.42 to -0.02)	0.032
Left atrial width (cm)	623	-2.86 (-5.5 to -0.22)	0.034
NYHA class (2-4 points)			
LVEDVi (ml/m ²)	591	-0.02 (-0.03 to 0)	0.025
LVESVi (ml/m ²)	591	-0.04 (-0.06 to -0.01)	0.003
LVEDD (cm)	644	0.35 (0.05 to 0.66)	0.022
LVESD (cm)	644	0.38 (0.03 to 0.74)	0.035
LVEF (%)	651	0.02 (0 to 0.05)	0.029
E/A ratio	403	0.32 (0.04 to 0.6)	0.023
Septal e'	379	0.09 (0 to 0.18)	0.049
Left atrial width (cm)	644	0.38 (0.1 to 0.65)	0.007
Global LS	338	-0.07 (-0.14 to 0)	0.042

Legend: QoL, quality of life; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; PVR, pulmonary vascular resistance; LS, longitudinal strain.

All models adjusted on age and sex.

Table 3. Association between health-related quality of life measures, cardiac and extra-cardiac factors in multivariable models

QoL measure	N	Beta coef. (95%CI)	P-value
Overall Summary Score (0-100 points)	490		
Body mass index (Kg/m ²)		-0.74 (-1.02 to -0.47)	<0.001
LVEDVi (ml/m ²)		0.19 (0.05 to 0.33)	0.007
Diabetes (yes)		-6.01 (-10.05 to -1.97)	0.004
Heart rate (bpm)		-0.20 (-0.37 to -0.02)	0.025
Asthma (yes)		-6.78 (-13.52 to -0.04)	0.049
Clinical Summary Score (0-100 points)	490		
Body mass index (Kg/m ²)		-0.70 (-0.97 to -0.43)	<0.001
LVEF (%)		-0.41 (-0.66 to -0.17)	0.001
Heart rate (bpm)		-0.29 (-0.46 to -0.12)	0.001
Diabetes (yes)		-5.44 (-9.39 to -1.48)	0.007
Non-White race		-5.30 (-9.94 to -0.66)	0.025
VAS scale (0-10 points)	489		
Body mass index (Kg/m ²)		-0.58 (-0.81 to -0.35)	<0.001
LVEF (%)		-0.32 (-0.54 to -0.11)	0.003
Previous MI (yes)		-5.05 (-8.71 to -1.39)	0.007
NYHA class (2-4 points)	494		
Previous HF hosp.		-0.87 (-1.30 to -0.45)	<0.001
Age >75yr		0.93 (0.47 to 1.39)	<0.001
Diabetes (yes)		0.86 (0.42 to 1.29)	<0.001
Body mass index (Kg/m ²)		0.06 (0.01 to 0.10)	0.011
Atrial fibrillation (yes)		0.50 (0.04 to 0.95)	0.032

Legend: QoL, quality of life; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

Figure 1. Correlation between KCCQ-23 OSS and echocardiographic parameters in men and women

Legend: OSS, overall summary score; LVEF, left ventricular ejection fraction; LA, left atria; GLS, global longitudinal strain.

Spearman Rho:

OSS / LVEF: men = -0.09, P =0.091; women = -0.01, P =0.87.

OSS / Septum thickness: men = -0.07, P =0.20; women = -0.20, P =0.001.

OSS / LA width: men = -0.10, P =0.084; women = -0.04, P =0.51.

OSS / GLS: men = 0.06, P =0.44; women = -0.04, P =0.62.