Right Ventricular Myocardial Strain in Patients having Heart Failure with Preserved Ejection Fraction enrolled in the PARAGON-HF trial

by

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Overview

Heart Failure Preserved Ejection Fraction

Heart failure with preserved ejection fraction (HFpEF) is associated with excess morbidity and mortality(1-7). There are approximately 900000 new cases of heart failure annually(8), of which more than half are attributable to HFpEF(1, 2, 4, 5). Moreover, the prevalence of HFpEF seems to be on the rise(7, 8). Five-year costs and survival are similar to patients with HF with reduced ejection fraction (HFrEF). However, there is a disparity in the available evidence between HFpEF and HFrEF. The dearth in evidence can be traced to the V-HeFT study findings which led to a consensus to exclude patients with normal ejection fraction from clinical trials having mortality as endpoint(9). To date, approximately three decades later, consensus on HFpEF has changed but there is yet to be a proven effective therapy for HFpEF patients(8, 10-12). Figure 0.1 displays the natural history of clinical trials in heart failure following the V-HeFT study. PARAGON-HF trial was the most recently completed trial in May 2019.

Right ventricle in brief

The right ventricle has a complex morphology due to its noncylindrical form and exhibits different hemodynamic qualities compared to the left ventricle (13, 14). There is a predominance of longitudinal and oblique myofibers in the RV free wall. However, its contraction pattern incorporates different motion components along three anatomically relevant axes:

(1) longitudinal shortening with traction of the tricuspid annulus towards the apex, (the focus of most conventional echocardiographic techniques)

(2) radial motion of the free wall often referred to as “bellows effect”, and

(3) anteroposterior shortening of the chamber y stretching of the free wall over the septum.

Conventional echocardiographic methods of RV functional assessment focus on longitudinal shortening. Advanced imaging techniques such as speckle tracking(13, 15-22) and 3D echocardiography allow an in-depth characterization of mechanical patterns, providing better

understanding of RV systolic and diastolic function.

The right ventricle has recently been gaining a lot of research consideration in HFpEF(4, 5). Cardiac magnetic resonance is considered the gold standard for imaging the right ventricle but is limited by cost and availability(13, 15, 16, 19, 23-27). Echocardiography is the recommended first-line diagnostic technique for the assessment of the right ventricle and right atrium. RV systolic function assessed by several conventional measurements are recommended according to guidelines, but the efficacy of these parameters as diagnostic and prognostic tools have been questioned by many experts.

Conventional RV systolic measurements such as tricuspid annular plane systolic excursion (TAPSE and RVFAC) are the most frequently reported(4) and have been shown to be predictive of all-cause death(4, 17, 22, 28). They have several limitations which may be overcome by right ventricular myocardial strain analyses(16, 19). However, there are limited reports on RV myocardial strain despite high recommendation by experts.

Myocardial strain refers to the deformation (shortening, lengthening, or thickening) of the myocardium through the cardiac cycle. Myocardial strain can be measured by tissue Doppler imaging or, more recently, speckle tracking echocardiography. Speckle-tracking echocardiography uses imaging software to assess the movement of specific endocardial segments of heart that are recorded in standard echocardiograms. It is proposed that a reduction in myocardial strain may indicate sub-clinical impairment of the heart and can be used to inform treatment before development of symptoms and irreversible myocardial dysfunction. Myocardial deformation imaging techniques were developed to assess LV function. However, it has recently been applied to the right heart and gained increased appreciation for the potential of deeper evaluation and exploration of the importance of RV. RV deformation imaging is clinically useful in other cardiovascular conditions (19, 21, 26, 29) but the value of this new tool has been less well explored in heart failure preserved ejection fraction (HFpEF).

Unmet need and clinical implications of RVD in HFpEF

Heart failure with preserved ejection fraction is associated with poor outcomes and a huge problem globally. HFpEF is heterogenous, and to date, there are limited therapeutic options despite our increasing understanding of its pathogenesis. Identifying patients at risk of adverse outcomes and intensive therapy is still the best management strategy adopted. Despite its heterogenous nature, right ventricular dysfunction has been increasingly identified as common in HFpEF. RV dysfunction is usually linked to load dependent conditions such as pulmonary hypertension which is also quite frequent in HFpEF. However, RV remodeling may also occur independent of pulmonary pressures and may also be linked to load independent conditions such as diabetes, obesity and atrial fibrillation. The prevalence and prognostic value of RV dysfunction in HFpEF have been widely but variably reported. The prognostic value is still debatable, as some studies have observed associations with poor prognosis and others were not able to observe these associations. Moreover, most the studies reporting RV dysfunction in HFpEF used conventional echocardiographic RV systolic measurements which has known limitations such as angle and load dependence. RV myocardial strain is a relatively novel, feasible, reproducible and effective measure of RV that is less susceptible to limitations of conventional RV measurements. Nevertheless, there are limited studies on RV myocardial strain in HFpEF. Given these, we aimed to analyze RV myocardial strain and its prognostic value in a clinical trial of patients with heart failure preserved ejection fraction having primary endpoint as heart failure hospitalization and cardiovascular mortality.

Summary of approach

Right ventricular function estimated by right ventricular myocardial strain is the focus of this

manuscript. In chapter 1, we describe findings of a study that analyzed the usefulness of RV myocardial strain measurements to accurately detect abnormal conventional RV function echocardiographic measurements. We specifically aimed at investigating impaired RV global (RVGLS) and free wall longitudinal strain (RVFWLS) despite normal conventional RV systolic indices (RVFAC & TAPSE). We investigated the relationship between left ventricular (LV) and right ventricular (RV) systolic function to RVGLS and RVFWLS. We also analyzed the association of right ventricular myocardial strain to cardiovascular hospitalization and all-cause deaths. Chapter 3 focuses on a similar cohort of patients as in chapter 1. In chapter 2, we specifically aimed at describing RV free wall longitudinal strain and association to baseline and echocardiographic features based on subgroups of RVFWLS tertiles. We then tested the association of RVFWLS to the primary outcome of the clinical trial (first, recurrent heart failure hospitalization, and cardiovascular death). Associations were tested both as continuous RVFWLS or categories according to tertiles of RVFWLS.

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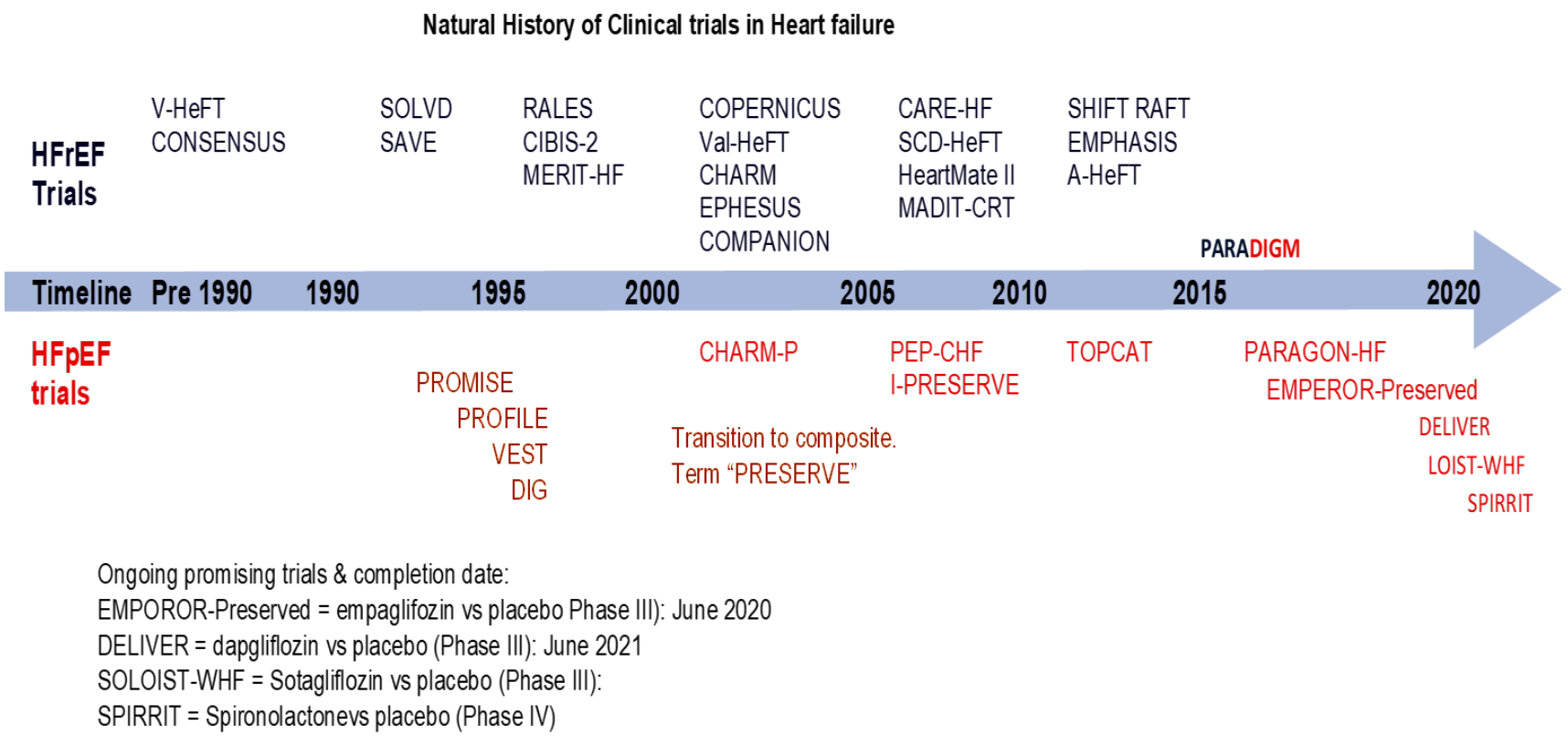

Figure 0.1 Natural History of Heart Failure Clinical Trials.

Paucity of clinical trials since V-HeFT consensus. Earliest trial in HFpEF CHARM-P was a sequel to a HFrEF trial CHARM. Approximately at this same time, the term "PRESERVED" ejection fraction started gaining recognition. PARAGON is the most recent trial in HFpEF completed in MAY 2019. Yet no currently effective therapy. Promising trials in the coming years include EMPEROR-Preserved, DELIVER, SOLOIST-WHF and SPIRRIT which will be completed in within a 2-year margin from PARAGON-HF

CHAPTER 1. Subtle right ventricular systolic abnormalities in PARAGON-HF: Insights from conventional and speckle tracking echocardiography in patients with HFpEF

Usefulness of right ventricular myocardial strain in detecting subclinical RV systolic abnormalities and its association to cardiovascular hospitalization and all-cause mortality in patients with heart failure preserved ejection fraction

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Abstract;

Aim: To describe the usefulness of right ventricular (RV) myocardial strain in detecting RV systolic abnormalities; predicting cardiovascular hospitalization and all-cause mortality in patients having heart failure preserved ejection fraction enrolled in the PARAGON-HF (Prospective comparison of ARnI with Arb Global Outcomes in heart failure with preserved ejectioN fraction)

Background: RV myocardial strain has been shown to be a feasible and reproducible estimate of RV function that is less susceptible to angle and load dependence, which are major limitations of conventional echocardiographic methods. However, compared to conventional methods, there is limited evidence on the use of RV deformation imaging in HFpEF.

Methods: Of 834 participants of PARAGON-HF with at least one conventional RV function estimate [tricuspid annular plane systolic excursion (TAPSE <1.6cm) or RV fractional area change (RVFAC <35%)], 527 had measurable RV global longitudinal strain (RVGLS) and free wall longitudinal strain (RVFWLS). Conventional RV dysfunction was in accordance with guidelines while impaired RV myocardial strain was defined as RVGLS >-17% and RVFWLS >-19%. We analyzed correlates, receiver operator characteristic area under curve of RVGLS and RVFWLS for accuracy to detect abnormal TAPSE and RVFAC. Cox regression was used to test associations to cardiovascular hospitalizations and/or all-cause death.

Results: RV systolic abnormalities estimated by myocardial strain (RVGLS, 58.9%) and (RVFWLS, 53.6%) were more frequent than estimated by RVFAC (8.5%) TAPS (31.5%). Despite normal TAPSE and RVFAC, at least half the patients had abnormal RVGLS and RVFWLS. There was no significant difference in accuracy to detect abnormal RVFAC and TAPSE, however, RVGLS had a higher sensitivity, while RVFWLS had a higher specificity. LV systolic function had peak correlations in septal wall and troughed in free wall segments. Survival was worse in patients with abnormal RVFWLS. There was a significant crude association of increasing mortality per 1% increase in RV myocardial strain which was more apparent in RVFWLS (HR (95%CI): 1.03 (1.01,

1.06) p=0.058). This association was less apparent in RVGLS (1.02 (0.99, 1.05) p=0.24).

Conclusion: Conventional RV measurements underestimate the presence of RV abnormalities. RVFWLS is a more accurate measure of RV systolic function and less influenced by LV systolic dysfunction compared to RVGLS. RVFWLS was crudely associated with all-cause mortality in HFpEF. Further studies are needed to validate these findings.

Key words: right ventricle, heart failure, longitudinal strain, all-cause mortality, cardiovascular hospitalization

Word count: 360

Key Messages (Highlights)

1. Right ventricular systolic abnormalities are underestimated by conventional echocardiographic measurements compared to RV global or free wall longitudinal strain. Abnormalities in RV myocardial strain are present in at least 1 of 2 HFpEF patients, even when conventional measurements (TAPSE, RVFAC and RV systolic pressure) are normal. This further suggests the presence subclinical changes in the RV systolic function

2. Both RV global and free wall longitudinal strain similarly predict abnormalities in normal conventional echocardiographic measurements (RVFAC and TAPSE). However, RV free wall longitudinal strain (RVFWLS) was more specific and less influenced by left ventricular systolic function compared to RV global longitudinal strain (RVGLS)

3. Incidence and risk of cardiovascular hospitalization and all-cause mortality are more apparently associated to increases in RV free wall longitudinal strain (RVFWLS); meanwhile these associations are less apparent with increases in RV global longitudinal strain (RVGLS)

Word count: 4341

Introduction

Right ventricular (RV) dysfunction is quite common in heart failure with preserved ejection fraction (HFpEF), however, the prevalence varies widely(1-7). RV dysfunction is present in about one – third, potentially up to half patients with HFpEF(2, 3). The extent to which the presence of abnormal RV function varies in HFPEF studies may be due to factors inherent to the RV or HFpEF as a disease.

HFpEF is a heterogenous clinical syndrome(8, 9), mainly defined by a preserved left ventricular ejection fraction (LVEF). Phenotypic variation in HFpEF may be associated with differences in cardiac profiles and prevalence of RV dysfunction(2, 3, 8). More so, different cut-offs for definition of HFpEF in published studies (LVEF >40%, >45% and >50%) are an additional challenge for estimating the exact prevalence of RVD. Load-dependent comorbidities such as pulmonary hypertension and renal impairment are frequent in HFpEF(10, 11). Conventional echocardiographic indices of RV structure and function are load- and angle-dependent(12, 13). Thus, may inaccurately estimate RV dysfunction in HFpEF.

The RV has a complex geometry and is relatively difficult to evaluate (14). The gold standard for non-invasive RV quantification and assessment is cardiac magnetic resonance imaging (CMRI) but has limited utility in clinical setting due to cost and operator time(1, 10, 15). Echocardiography is relatively affordable, widely used and several conventional estimates of RV function have been reported to correlate with CMRI. RV fractional area change (RVFAC) and TAPSE (Tricuspid annular plane systolic excursion) are the most reported conventional echocardiographic estimates of RV function(3). Disparities in use of RV echocardiographic measurements and cut-offs have made the estimation of prevalence of RVD a challenge.

RV myocardial strain by speckle tracking imaging is a relatively novel and effective RV systolic function estimate(7, 15, 16). RV myocardial strain correlates with CMRI(1) and less susceptible to angle-/load-dependence, which are known limitations of conventional echocardiographic RV

function estimates(16). There is limited evidence on the extent to which conventional echocardiographic assessment of RV function inaccurately estimates RV dysfunction. We thus, conducted RV myocardial strain imaging analyses in patients with HFpEF. We aimed to investigate the presence of impaired right ventricular longitudinal strain despite normal or preserved RV conventional measurements; as well as, its association to cardiovascular hospitalization and all-cause deaths.

Methods

Design

This was a pre-specified secondary analysis of patients having HFpEF enrolled in PARAGON-HF (Prospective comparison of ARnI with Arb Global Outcomes in heart failure with preserved ejectioN fraction) trial. The rationale, methods and description of baseline, clinical and echocardiographic profile of patients in PARAGON-HF trial have been reported(6, 17). Following termination of the trial, we conducted a sub-study focused on investigating longitudinal systolic strain of RV in PARAGON participants with available cardiac imaging.

Patients

PARAGON-HF was a multicenter, international, randomized double-blind, event-driven trial testing the long-term efficacy and safety of sacubitril-valsartan compared with valsartan alone in adult patients with signs and symptoms with HF and left ventricular ejection fraction (LVEF ≥45%). Briefly, the primary outcome of PARAGON-HF was a composite of first or recurrent HF hospitalization or cardiovascular death. Sacubitril valsartan was not shown to be an effective treatment for reducing primary outcome in patients having HFpEF. Details of design, rationale, methods and study results of the trial were recently published(17, 18).

PARAGON-HF enrolled 4822 patients from 173 sites in 43 different countries who met the following criteria: age ≥ 50years, left ventricular ejection fraction (LVEF) ≥45%, had current

symptomatic HF requiring diuretics for ≥ 30days (NYHA II – IV), structural heart disease and an elevated NT-proBNP.

Echocardiography

Baseline echocardiograms blinded to clinical information were obtained from site investigators and uploaded to PARTNERS online platform and imaging database of the Cardiac Imaging Core Lab (CICL), Brigham and Women's Hospital, Boston, USA. Conventional echocardiographic assessment of LV and RV structure and function were conducted by trained and dedicated technicians offline at the CICL. Quantification of echocardiographic estimates were performed with respect to American Society of Echocardiography guidelines(13, 19). Quantitative measures for both the left and right ventricular structure and function were analyzed. Details of baseline echocardiographic characteristics and associations to primary outcomes have been published(6).

Conventional estimates of RV function

Of 1087 participants of PARAGON-HF having cardiac images, 834 had at least one conventional two-dimensional echocardiographic estimate of RV structure and systolic function. In PARAGON-HF, conventional estimates of RV function were tricuspid annular plane systolic excursion (TAPSE), right ventricular fractional area change (RVFAC), right ventricular myocardial performance index (RVMPI), tricuspid regurgitant peak systolic velocity (TRV). Right ventricular systolic pressure (RVSP) was calculated as RVSP (mmHg) = 4 * $(TRV)^2$ + 5mmHg. Abnormalities in baseline conventional echocardiographic estimates have been reported by Shah et al previously(6). Conventional RV systolic estimates of choice for our study were RVFAC and TAPSE. These are the most reported conventional two-dimensional echocardiographic estimates of RV function and have been shown to have prognostic relevance in HFpEF.

Strain imaging analysis

RV myocardial longitudinal strain analyses were performed offline on available echocardiograms at the CICL. Speckle-tracking echocardiography conducted using TOMTEC Imaging systems (Image-Arena version 4.6.6.3). We identified one cardiac cycle; a selected R-R interval as defined by the QRS complex or frame by mitral & tricuspid valve closure. Followed by a tracing of the endocardial border of right ventricle in patients with a RV-focused apical-4-chamber view of the heart. Semiautomatic analyses of longitudinal strain in basal, mid and apical segments of both RV lateral free wall and interventricular septum were computed. RV global longitudinal strain (RVGLS) was computed as the mean peak longitudinal strain value in all six segments i.e. basal, mid and apical segments of both lateral free wall and interventricular septum. RV free wall longitudinal strain (RVFWLS) was the mean peak longitudinal strain in basal, mid and apical segments of the lateral free wall of RV (Figure 1.1). Of 834 patients with at least RVFAC or TAPSE on echocardiograms, 527 were analyzed for right ventricular global (RVGLS) and free wall longitudinal strain (RVFWLS).

RV myocardial longitudinal strain reproducibility:

At the CICL, one of the authors was trained to conduct RV myocardial strain to satisfactory standards. Satisfactory reproducibility of investigator's measurements of RV myocardial strain were an intraclass correlation (ICC) of $\geq$0.9 and coefficient of variation (CoV) of less than 10% in 3 sets of 20 blinded echocardiograms compared to CICL standards. The satisfactory reproducibility of investigator is reported in Table 2.7

Definitions

Abnormal conventional estimates of RV systolic function were RVSP>39 mmHg, TAPSE <1.6cm

and RVFAC <35% consistent with guidelines and consensus by experts(12, 13). Guidelines recommend abnormal RV myocardial strain as RVFWLS >-20% but no reference cut-offs for RVGLS(12). We defined abnormal RV myocardial strain as RVFWLS >-17% and RVGLS > -19% consistent with findings by Morris et al based on a cohort of HFpEF and normal patients(7). Subclinical or subtle RVD was defined as impaired right ventricular myocardial strain (RVGLS>-17% & RVFWLS>-17%) despite normal conventional 2D estimates of RV systolic function (TAPSE>1.6cm, RVFAC>35%). Outcomes of interest were cardiovascular hospitalization and all-cause death during follow-up period in PARAGON-HF trial.

Statistical analyses

Continuous data are expressed as mean ± standard deviation (SD). Categorical data are presented as frequencies and percentages. Bar charts were used to show spectrum of RV dysfunction in our study population per RV systolic function measurement. Spearman correlation were used to evaluate relationship between RV myocardial strain and baseline characteristics, conventional echocardiographic indices of right and left ventricular function. Area plots were used to illustrate trend in correlation of LV function to segmental longitudinal strain of the RV. Area under the curve for receiver operating characteristic (AUC) were estimated, plotted and compared to show discrimination of RVGLS and RVFWLS for abnormal RVFAC and TAPSE. Also, cox regression was used to test association of exposure (RVGLS and RVFWLS) to outcomes; cardiovascular hospitalization (CVH) and all-cause death in HFpEF. Restricted cubic splines with 4 knots were used to show trend in continuous association between all RV systolic function estimates and outcome events over follow-up time. Following crude associations, we accounted for age, gender and right ventricular systolic pressures or pulmonary pressures in cox regression models. Dichotomous association of abnormal RVFLWS and RVGLS to outcomes were illustrated using Kaplan Meier survival estimates and trend curves.Two-sided tests with $p<0.05$ were

considered as significant. Stata 14 was used for data analyses.

Results

Figure 1.2 shows consort flow chart of patients included in our study analyses. Of 4822 participants enrolled in PARAGON-HF, 1087 had cardiac images and 834 echocardiograms had at least one right ventricular fractional area change (RVFAC) or tricuspid annular place systolic excursion (TAPSE) or tricuspid regurgitant peak jet velocity (TRV). Of these, 209 had missing and unclear focused right ventricular apical-four-chamber view. Finally, 527 patients enrolled in PARAGON had reliable RV myocardial strain estimated by RV global and/or free wall longitudinal strain were included in the study analyses.

Baseline clinical characteristics

Mean age of 527 participants was 74±8 years with a slight female predominance (56.5%). Patients were mainly white (79.5%), Asian (15.6%), and Black or African American (4.2%). Patients were enrolled mainly from North America (36.4%), Western Europe (26.4%), Central Europe (18.8%), Asia (18%) and Latin America (0.4%). Spectrum of RVGLS values ranged from -31.6 to -1.3 with a mean RVGLS of -15.5 ±5.7 and median (interquartile range: IQR)) of -15.6 (-19.7, -11.2). (

Table 1.1) Spectrum of RVFWLS ranged from -31.6 to -1.9 with a mean RVFWLS of -18.9 and a median (IQR) of -18.5 (-23.1, -14.3). (Figure 1.3)

There were marked differences in baseline and clinical characteristics comparing patients with or without RV myocardial strain analyses. Patient group having RV myocardial strain analyses were older (74.3 ± 7.9 vs 72.6 ± 8.5, p=0.001) and had a higher baseline creatinine (101 ± 29 vs 96 ±

27, p=0.001) and ejection fraction from study site (58.7 ± 7.5 vs 57.4 ± 7.9, p=0.001). Patients with RV myocardial strain had a lower percentage of female gender (56.5 vs 51.1%, p=0.02), hypertension (93.2 vs95.9%, p=0.004) and diabetes (36.2 vs 43.8%, p=0.001). Patients with RV myocardial strain had a lower mean systolic blood pressure (128 ± 16 vs 131 ± 15, p=0.001), heart rate (69 ± 12 vs 71 ± 12, p=0.005) and body mass index (29.3 ± 4.9 vs 30.3 ± 5.0, p=0.001) (

Table 1.1).

Baseline echocardiographic features

Table 1.2 shows baseline echocardiographic features comparing patients having RV myocardial strain analyses to patients having cardiac images with RV myocardial strain. Many of the baseline echocardiographic features were similar between the two groups. Patients with RV myocardial strain analyses had lower left ventricular end-diastolic dimensions (4.5 ± 0.7 vs 4.7 ± 0.6, p=0.001), lower left atrial dimensions (4.2 ± 0.7 vs 4.3 ± 0.6, p=0.05), higher mitral peak early diastolic wave velocity (E wave, cm/s; 92 ± 28 vs 87 ± 28, p=0.007), higher right ventricular fractional area change (RVFAC, %; 47.4 ± 9.2 vs 45.2 ± 9.4, p=0.03); and a lower right ventricular end-systolic area (RVESA, cm^2; 11.1 ± 4.0 vs 12.0 ± 4.7, p=0.03) (Table 1.2)

Prevalence of right ventricular dysfunction and subtle right ventricular systolic abnormalities despite normal conventional echocardiographic measurements

Right ventricular dysfunction is defined as at least one abnormal measure of RV systolic function echocardiographic parameter. Figure 1.4 shows the spectrum of right ventricular dysfunction per

estimate of RV function. The prevalence of RV dysfunction ranged from 8.9% (RVFAC), 24.6% (right ventricular systolic pressure), 31.6% (TAPSE), 53.6% (RVFWLS) and 58.9% (RVGLS). Preserved RV conventional measurements were determined according to the recommendations of the EACVI (i.e. RVFAC≥35%, TAPSE≥1.7cm, and TRV<2.9cm/s or RVSP<39mmHg). Figure 4 shows the spectrum of abnormal RV myocardial strain despite normal conventional echocardiographic RV systolic function measurements. Despite normal RVFAC, TAPSE and TR velocity, the prevalence of abnormal RVFWLS was 50.6%, 50.8% and 53.6% respectively. Abnormal RVGLS was present in 55.2%, 53.6% and 63.9% of patients with normal TAPSE, RVFAC and TR velocity (or RVSP) respectively. (Figure 1.5)

Baseline, LV and RV systolic Correlates of right ventricular myocardial strain

RV global and RV free wall systolic strain were significantly linked to heart rate, body mass index (BMI). Creatinine correlated significantly with RVFWLS (R=+0.14, p=0.002) but not RVGLS (R=+0.06, p=0.19). However, glomerular filtration rate (GFR) did not correlate with either RVFWLS or RVGLS. There were modest significant correlations between LV systolic function measurements to RVGLS and RVFWLS. Compared to RVFWLS, RVGLS had a slightly higher estimated R coefficient of correlation for apical 4-chamber LVGLS (0.39 vs 0.33) and apical 2-chamber LVGLS (0.39 vs 0.31). Meanwhile, many of the RV systolic function estimates were more significantly linked to RV FWLS compared RVGLS. RV end-diastolic area was significantly correlated with RVFWLS (0.09, p=0.04) and not RVGLS (+0.07, p=0.09). Figure 1.6 shows the trend in relationship between RV systolic function and segmental strain which peaks in free wall segments but troughs in septal wall segments. Comparing RVFWLS to RVGLS, R coefficients were slightly higher for TAPSE (0.33 vs 0.28), RVFAC (0.31 vs 0.23), RV end-systolic area (0.23 vs 0.17) and RV myocardial performance index (-0.18 vs -0.23) (Table 1.3). Figure 1.6 illustrates trends in correlation (R) coefficient of LV systolic measurements with per segmental longitudinal

strain across regional segments of the right ventricle. R coefficients of correlation between LV systolic function and longitudinal strain peaks in septal wall segments (basal, mid, apical) and troughs in lateral free wall segments. The relationship between LV systolic function and RV strain decreases moving from septal wall to free wall. Trend was similar for individual or mean LV systolic R coefficients.

Accuracy of RV myocardial strain measurements to detect abnormal RV conventional systolic function measurements (TAPSE and RVFAC)

Figure 1.8 shows sensitivity and specificity of RV myocardial strain to detect abnormalities in conventional RV echocardiographic systolic indices (RVFAC and TAPSE). RVGLS had a higher sensitivity for both abnormal TAPSE (76.8 vs 67.4%) and RVFAC (82.9 vs 80.5%), while RVFWLS was more specific for abnormal TAPSE (49 vs 44.9%) and RVFAC (49 vs 43%). Comparing equality of receiver operating characteristic area under the curve (AUC), the ability of RVFWLS to detect abnormal RVFAC and TAPSE was not so different from RVGLS to predict patients as having abnormal or normal RVFAC and TAPSE. Nevertheless, the RVFWLS AUC were slightly higher than RVGLS AUC; Abnormal TAPSE (0.61 vs 0.60, p=0.33) and abnormal RVFAC (0.66 vs 0.64, p=0.40) (Figure 1.9)

RVD myocardial strain, cardiovascular hospitalization and all-cause death in HFpEF

In 527 participants included in our study, there were a total of 212 cardiovascular hospitalizations and 73 all-cause deaths during trial follow-up. The incidence of cardiovascular hospitalization and CV death were significantly higher in groups with abnormal RVFWLS but not RVGLS (Table 1.6). In both continuous and stratified analyses, RVGLS and RVFWLS were not significantly associated with cardiovascular hospitalization. There was a linear trend for increase in crude incidence rate of all-cause mortality for every 1% increase in RVFWLS which did not reached conventional levels of statistical significance (crude HR: 1.03 (1.01, 1.06) p=0.058) (Figure 1.10). Comparing crude Kaplan-Meier survival estimates, group of patients with normal RVFWLS had significantly better

survival over time compared to group with abnormal RVFWLS (p=0.04) (
Figure 1.11). Compared to group with normal RVFWLS, group with abnormal had a higher incidence and risk of death that did not reach statistical significance [crude HR (95% CI1.40 (0.97, 2.02) p=0.07] (Table 1.4,
Figure 1.11).

Discussion

In a cohort of 527 patients with heart failure preserved ejection fraction enrolled in PARAGON-HF, we observed the prevalence of abnormal RV dysfunction varied by RV systolic echocardiographic estimate. Despite normal RVFAC, TAPSE and RVSP, impaired RVFWLS were present in approximately half of patients. Meanwhile, abnormal RVGLS was present in approximately one-half to one-third of patients with normal TAPSE, RVFAC and TRV. We also observed baseline, clinical and cardiac factors were significantly linked to RV global and free wall systolic strain. RV global systolic strain was slightly better linked to left ventricular systolic function while RVFWLS was better linked to RV systolic function measurements. This was further reflected in septal wall segments having the highest correlation to left ventricular systolic function, while lateral free wall segments had the highest correlation with conventional RV systolic function measurements. The ability to detect and discrimination to stratify HFpEF patients to normal or abnormal TAPSE and RVFAC was not significantly higher in RVFWLS. Survival was lower in patients with abnormal RVFWLS. Crude associated with outcomes: cardiovascular hospitalization and all-cause deaths were more apparent with RVFWLS than RVGLS.

Prevalence of right ventricular systolic dysfunction (conventional & myocardial strain)

There is increasing evidence that RV dysfunction is frequent in patients with HFpEF(6, 9), but the exact prevalence is a challenge. We observed RV systolic abnormalities were present in approximately one-tenth (RVFAC), one-quarter (RVSP), one-third (TAPSE), one-half (RVFWLS) and two-thirds (RVGLS) of our study participants. Our findings are consistent with the trend found

in prior publications that report disparities in prevalence of RV dysfunction based on different RV echocardiographic measurements(5, 6, 11, 20-22). Gorter et al in a recent systematic review and meta-analyses, have suggested that on average RV dysfunction is present in about a third, and potentially up to half patients in HFpEF(2, 3). RV dysfunction estimated by RV myocardial strain (RVGLS & RVFWLS) were higher than estimated by abnormal RV conventional systolic estimates (RVFAC, TAPSE, RVSP). This may be because conventional echocardiographic measurements may inaccurately estimate RV function. In addition to limitations of angle and load dependence, conventional echocardiographic measures reflect the displacement or function in one segment of the right ventricle(15, 16, 23). Meanwhile, RV myocardial strain is angle and load-independent and provides an estimate of systolic function in both global and regional walls of the RV(1, 5). Thus, we considered RV conventional echocardiographic measurements underestimated RV dysfunction in HFpEF. It is well known that conventional RV echocardiographic may underestimate(23-25) RV function but the disparity is less well described.

Subtle or Subclinical RV systolic dysfunction detected by RV global and free wall systolic strain

Despite the limitation of conventional RV systolic measurements, RVFAC and TAPSE are the most widely used RV systolic function indices in clinical settings(5). We found that in patients with normal conventional systolic (RVFAC, TAPSE, RVSP), at least one-half had abnormal RV global and free wall strain (Figure 1.4). Per normal RVFAC, TAPSE and RVSP, RV systolic abnormalities were slightly more frequent using cut-offs of global RV strain compared to regional free wall systolic strain (Figure 1.4). There are limited reports on the extent to which RV myocardial strain is impaired despite preserved RV conventional measurements. Using same cut-offs for RV myocardial strain measurement, Morris et al reported a lower prevalence of abnormal RVGLS and RVFWLS in patients with normal TAPSE, RVFAC and Normal S' in in heart failure(7).

Compared to our study findings, abnormal RV systolic strain was less frequent in patients with normal TAPSE, RVFAC and S'. Our study population differed from that of Morris et al. The study by Morris et al included only Japanese and Germans, while ours is a multicenter trial with all races were included. However, Morris et al reported a similar prevalence of abnormal strain despite normal RVFAC and TAPSE in patients with HF reduced ejection fraction. A possible reason for the disparity of our study findings with that of Morris et al may be due to definition of LVEF. Morris et al defined HFpEF as LVEF cut-offs >50% while PARAGON-HF included patients with HFpEF based on LVEF>45%. Another possible reason is the use of different vendor software for RV myocardial strain analyses. We used TOMTEC Imaging systems while Morris and colleagues reported strain from use of Echo-Pac 113, GE software. A major limitation of strain analyses is the disagreement in strain measurements using different commercial software (24, 26). Nevertheless, using the same software RV strain is highly reproducible and has a better correlation with right ventricular ejection fraction estimated by CMRI compared to conventional RV measurements(1, 10, 15, 16, 27). Furthermore, global longitudinal strain has been shown to be superior to conventional systolic function measurements in identifying early left ventricular dysfunction(24, 25). Thus, RV global and free wall systolic longitudinal strain should be similarly considered to be valuable in detecting early or subclinical myocardial systolic dysfunction of the RV in patients with HFpEF.

Cardiac systolic measurements linked to RV myocardial strain

Our findings that LV and RV systolic factors were significantly linked to RV global and free wall strain is not unexpected (Table 1.3 & Figure 1.6). These are consistent with several studies that also found a significant interrelationship between the longitudinal systolic function of the right and left ventricle(28-30). RVGLS is an estimate of longitudinal systolic strain in both free wall and septal walls of the RV while RVFWLS is an estimate of regional systolic strain in segments of the

RV lateral free wall only(26, 31). In our analyses, conventional RV systolic function measurements were slightly better linked to RVFWLS, while LV systolic measurements were better linked to RVGLS. This is probably because of the septal component of RVGLS may influence from the left ventricle(32). Ventricular interdependence of RV to the LV maybe another reason why increasingly RVFWLS is favored over RVGLS as an estimate of RV myocardial strain. This is consistent with consensus by experts in guidelines, where RVFWLS is recommended over RVGLS as an accurate measure for RV longitudinal systolic strain(1, 12, 13, 16). This is further supported by our findings evaluating trend of correlation between LV systolic function measurements and RV segmental wall strain in our analyses. Relationship between LV systolic measurements and segmental wall longitudinal strain were peaked in region of septal wall, with a decreasing trend moving from septal wall segments to lateral free wall segments (Figure 1.6).

Accuracy of RV myocardial strain to detect abnormal RVFAC or TAPSE

For abnormal RVFAC, we observed that sensitivity was similarly high for both RVGLS and RVFWLS, and specificity was lower in RVGLS. It was remarkable that for abnormal TAPSE, RVGLS had a higher sensitivity but lower specificity compared to RVFWLS. The lower specificity of RVGLS is expected as we have previously observed that RVGLS may be more influenced by LV function in septal wall regions. Meanwhile, we also observed RVFWLS is better linked to RV function, probably the reason for the higher specificity for both RVFAC and TAPSE compared to RVGLS. RVFWLS and TAPSE both analyze the RV basal free wall, thus, the lower sensitivity of RVFWLS compared to RVGLS for abnormal TAPSE is somewhat unexpected. Although TAPSE is used widely in clinical practice and research(2, 5), it is inherently limited to only one-dimensional longitudinal displacement of the basal segment of lateral free wall. RV contraction is much more complex. Beyond contraction along longitudinal axis, radial and circumferential (anteroposterior) displacement and shortening occur simultaneously(33). There is paucity of data describing

relative contribution of radial and anteroposterior components of RV wall motion to global or regional systolic function. Longitudinal shortening seems to be the major determinant of RV contraction in normal persons(33). It is unclear if this is the same especially in HEFpEF, in there is high phenotypic variation(8, 9). Despite this, there is enough evidence on the prognostic value of TAPSE(4, 14, 21, 34, 35). Data on RV myocardial strain in HFpEF is limited and its prognostic relevance in HFpEF is not well established(5). However, RV myocardial systolic strain analyzes at least 3 segments (basal, mid, apical) of the RV as well as radial strain component. Therefore, we considered right ventricular myocardial strain may provide more insight into right ventricular mechanics beyond conventional echocardiographic measurements.

RV myocardial strain, cardiovascular hospitalization and all-cause death in HFPEF

In the present analyses, the trend of increasing incidence cardiovascular hospitalization or all-cause death during the study follow-up were more apparent with RVFWLS than RVGLS. Crude estimates of survival were apparently lower in group with abnormal RVFWLS and less so in group with abnormal RVGLS. We also observed an association of increasing incidence of all-cause deaths per 1% increase in RVFWLS within significant confidence intervals. HFpEF is a heterogenous condition with frequent comorbidities(9). Cardiovascular hospitalization and deaths may not be directly due to cardiac events. Several studies have reported that RV systolic function estimated by RVGLS is predictive of adverse outcomes in heart failure(1, 15, 26, 36) which is not so apparent in our analyses. Lejeune et al. in a Many of these studies have been conducted in patients who have end-stage heart failure or heart failure with severely reduced ejection fraction. These studies had lower mean RVGLS and used lower cut-offs in assessing associations to outcomes. Although morbidity and mortality are similar in HFpEF and HFrEF, the underlying mechanisms are not yet well understood(3). HFpEF is a heterogenous condition with no known effective. Furthermore, the etiology of right ventricular dysfunction in HFpEF may occur earlier in

HFpEF

Limitations

Some limitations should be considered following interpretation of our findings. Strain analyses were only feasible in about 50% of PARAGON echocardiographic studies, due to non-DICOM imaging format, missing views, and poor image quality. This may have limited our power to test associations. Strain analyses were conducted in echocardiograms with at least one conventional RV function estimate, this may have led to selection bias. However, there were minimal differences in echocardiographic features between group with echocardiograms with/out strain analyses. Cardiac Magnetic Resonance imaging (CMRI) is the gold standard for non-invasive assessment of the right ventricle. Cost and operator time limit the use of CMRI. Nevertheless, global longitudinal strain correlates better with CMRI than conventional RV measurements. We have reported the longitudinal contractile function of the RV; however, the RV contractile function occurs follows alignment in 3 axes: longitudinal, radial and anteroposterior displacement. Longitudinal displacement seems to be more contributive in normal healthy adults. It is unclear how contributive, radial or anteroposterior displacement contribute to RV function in HFpEF. Nevertheless, RV myocardial strain is angle and load independent, and consensus on value of radial strain assessment is not agreed on by all experts. Experience of operator is an important determinant to reproducibility of image analyses. However, investigator was trained to satisfactory standards of CICL whose reproducibility standards are published and have been used in many studies (Table 2.7). This study was conducted in a sub population of PARAGON-HF trial participants with very strict inclusion criteria for HFpEF. These may not represent the typical patient in community, thus, limiting the generalizability of our findings. However, we considered our findings valid in this sub group and of supplemental value in our understanding of RV dysfunction in HFpEF.

Conclusions

Presence of RV abnormalities varies depending on RV systolic parameter used. Conventional 2-dimensional echocardiography underestimated RV systolic abnormalities. We have observed that RV abnormalities measured by RV myocardial strain analyses were present in at least half of patients with HFpEF, even amongst those who have normal conventional systolic measurements. RVFWLS has a similar accuracy to detect abnormal RVFAC and TAPSE compared to RVGLS. However, RVGLS is more susceptible to LV systolic function due to septal component. We thus, suggest RVFWLS as a better or more specific measurement of RV systolic function. Increase incidence of all-cause mortality was associated with increasing RVFWLS and survival was worse in patients with abnormal RVFWLS. Given all these, we suggest RVFWLS as a more accurate measure of right ventricular function and may be associated with increase in risk of death. Further studies are needed to confirm the role of RVFWLS in predicting adverse outcomes in HFpEF.

Supplementary materials:

Supplementary materials are available at the end of manuscript

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Conflicts of interest: none

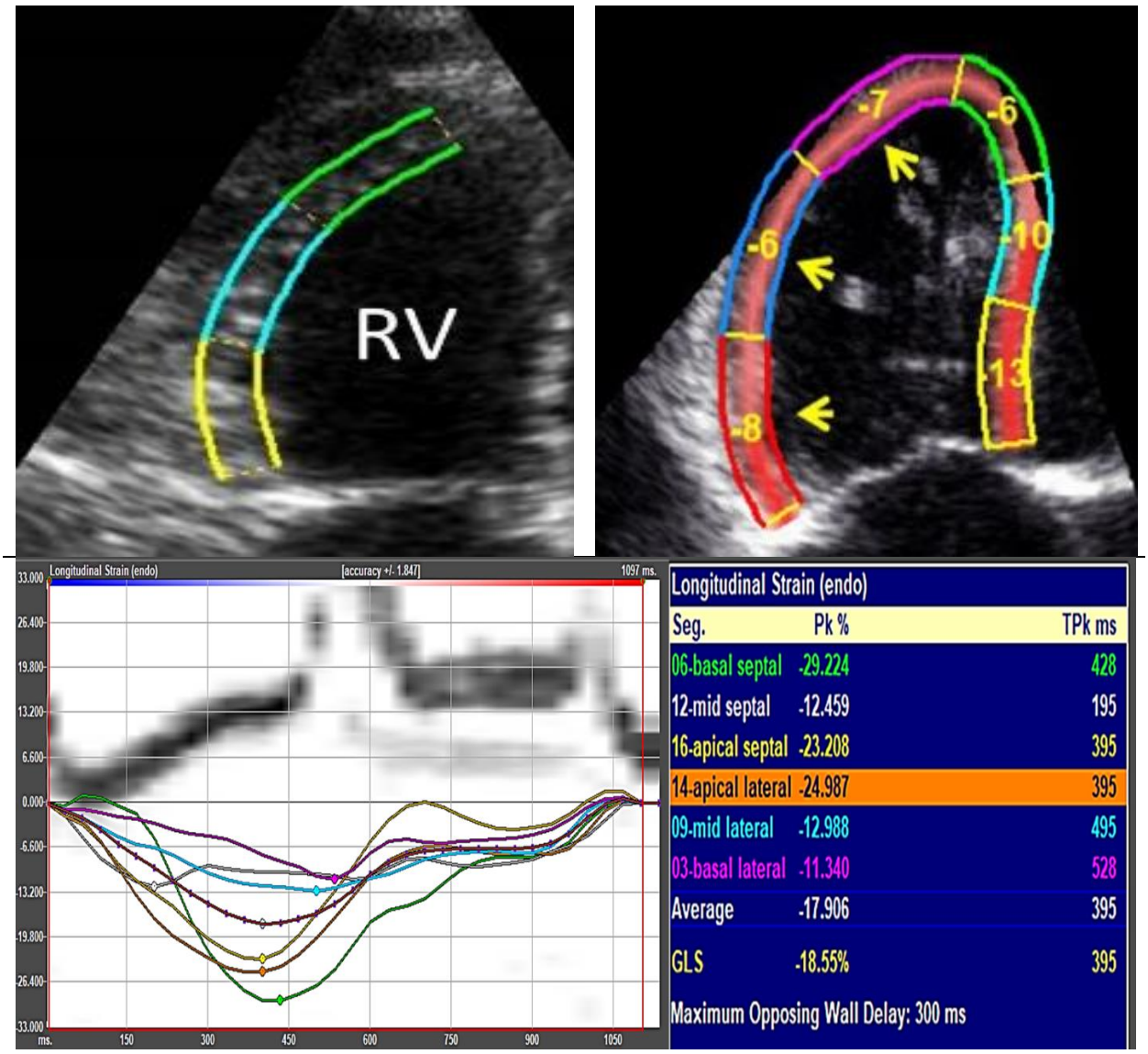


Figure 1.1: Illustration of speckle tracking imaging analyses

following endocardial tracing and tracking of basal, mid and apical segments of the right ventricle. RV regional systolic strain or Free wall strain (left: mean peak longitudinal strain in basal, mid and apical segments of Lateral free wall) and RV global systolic strain, RVGLS (right; mean peak longitudinal strain in all segments of lateral and septal wall)

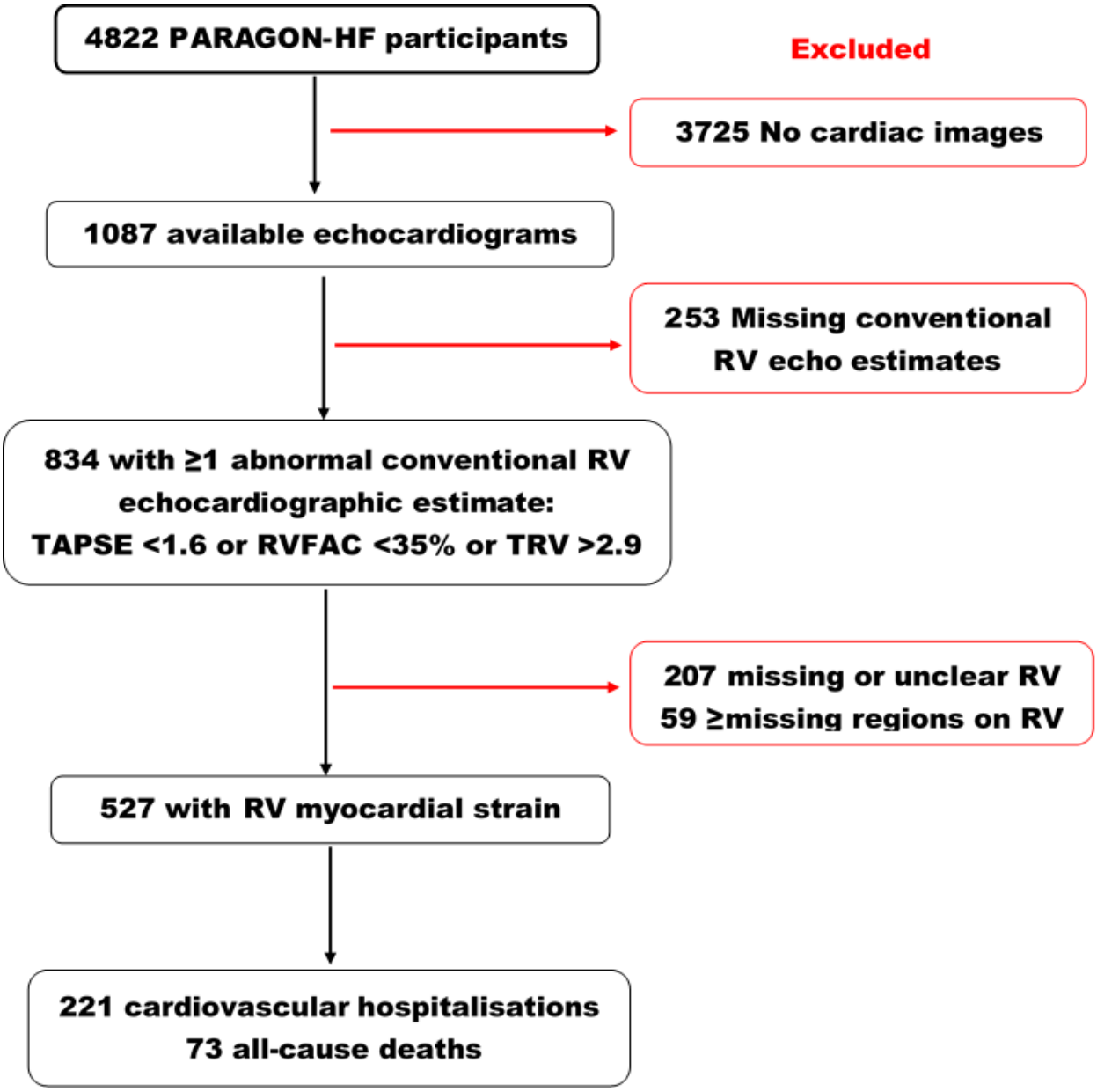


Figure 1.2: Consort Flow Chart for participants included and excluded in our study analyses

RV – Right ventricle/ventricular; TAPSE – Tricuspid Annular Plane Systolic Excursion; RVFAC – Right ventricular Fractional Area Change; TRV – Tricuspid Regurgitant peak jet velocity; RVGLS – right ventricular global longitudinal strain; RVFWLS – right ventricular free wall longitudinal strain

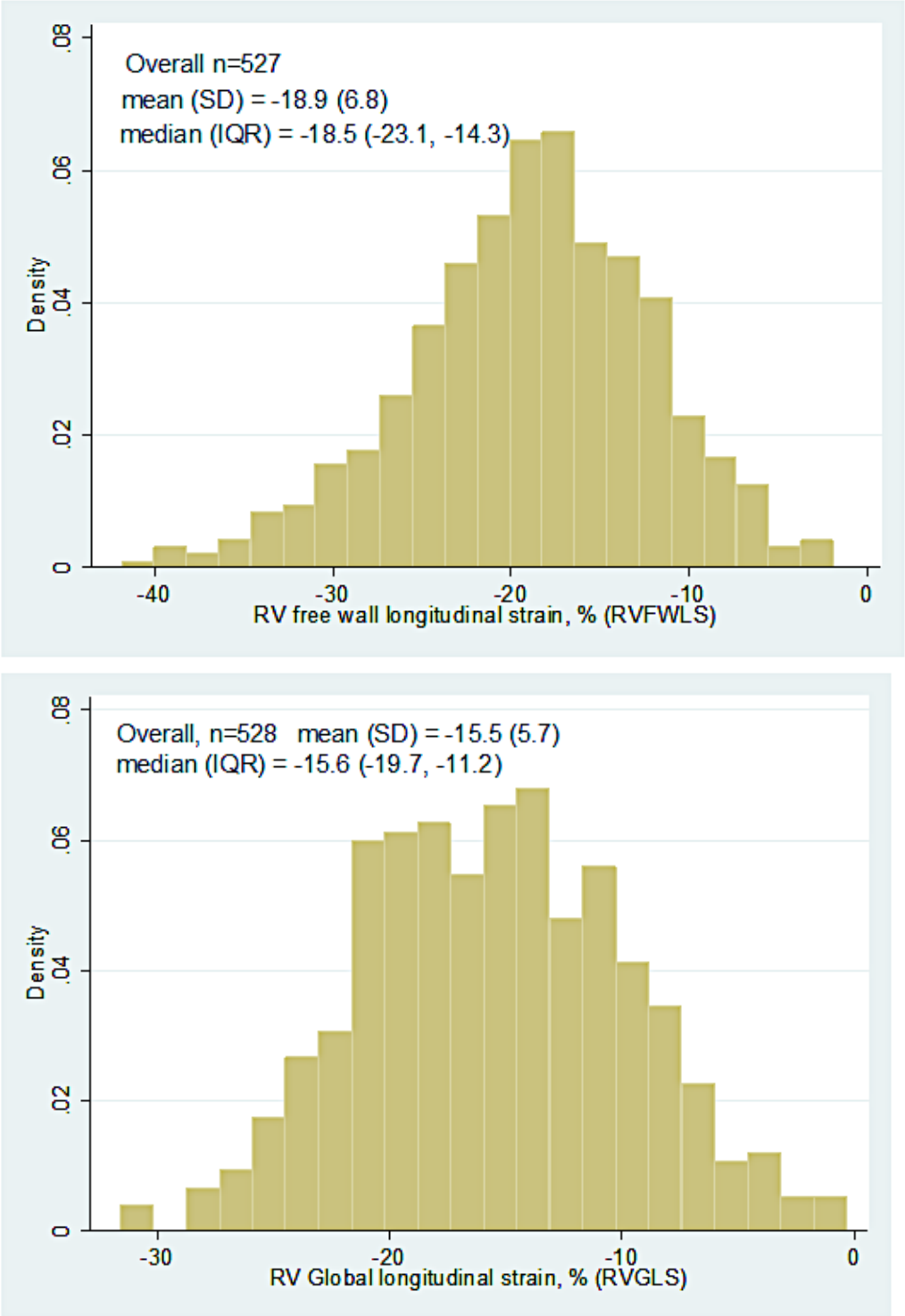


Figure 1.3: Histogram illustrating distribution of RV global and free wall longitudinal strain *(RVGLS: right)) and free wall longitudinal strain (RVFWLS: left)*

Table 1.1: baseline and clinical characteristics in PARAGON-HF participants included in our study (feasible RV myocardial strain measured) and those excluded due to no RV myocardial strain analyses.

Variables	Group with RV myocardial strain, n=527	PARAGON-HF with no RV myocardial strain, n=4269	p value
Age, years mean ±SD	74.3 ± 7.9	72.6 ± 8.5	0.001
Female, n (%)	298 (56.5%)	2181 (51.1%)	0.02
Race, n (%)			0.001
Asian	82 (15.6%)	525 (12.3%)	
Black or African American	22 (4.2 %)	80 (1.9 %)	
Other	4 (0.8 %)	176 (4.1 %)	
White	419 (79.5%)	3488 (81.7%)	
region, n (%)			0.001
Asia/Pacific and others	95 (18.0%)	667 (15.6%)	
Central Europe	99 (18.8%)	1616 (37.9%)	
Latin America	2 (0.4 %)	368 (8.6 %)	
North America	192 (36.4%)	367 (8.6 %)	
Western Europe	139 (26.4%)	1251 (29.3%)	
History of ischemic etiology, n (%)	152 (28.8%)	1571 (36.8%)	0.001
Atrial fibrillation, n (%)	181 (34.5%)	1371 (32.2%)	0.3
Diabetes, n (%)	191 (36.2%)	1871 (43.8%)	0.001

Hypertension, n (%)	491 (93.2%)	4093 (95.9%)	0.004
Stroke, n (%)	59 (11.3%)	449 (10.5%)	0.6
Prior HF hospitalization, n (%)	259 (49.1%)	2047 (48.0%)	0.6
MI, n (%)	107 (20.3%)	976 (22.9%)	0.19
NYHA, n (%)			0.68
2	383 (72.7%)	3065 (71.8%)	
3	142 (26.9%)	1175 (27.5%)	
4	2 (0.4 %)	29 (0.7 %)	
BMI, kg/m^2 mean ±SD	29.3 ± 4.9	30.3 ± 5.0	0.001
SBP, mmHg mean ±SD	128 ± 16	131 ± 15	0.001
Heart rate, bpm mean ±SD	69 ± 12	71 ± 12	0.005
Creatinine, mmol/L mean ±SD	101 ± 29	96 ± 27	0.001
NT-proBNP, geometric mean ±SD	6.8 ± 0.9	6.8 ± 0.9	0.39
Ejection fraction from screening site, n (%)	58.7 ± 7.5	57.4 ± 7.9	0.001

NYHA - New York Heart Association; BMI - Body Mass Index; MI - Myocardial infarction; HF-Heart failure

Table 1.2: Baseline echocardiographic features by PARAGON-HF participants having cardiac images with or without RV myocardial strain analyses

Variables	PARAGON-HF with RV strain, n=527	PARAGON-HF without RV strain, n = 560	p value
LV structure			
LVEDD, cm	4.5 ± 0.7	4.7 ± 0.6	0.001
LVEDV, cm3	101 ± 38	104 ± 38	0.26
LVESV, cm3	43 ± 22	45 ± 23	0.18
LVESD, cm	3.3 ± 0.7	3.3 ± 0.7	0.07
Septal wall thickness, cm	1.1 ± 0.2	1.1 ± 0.2	0.9
LV mass, g	168 ± 60	171 ± 55	0.36
LV mass index, g/m2	89 ± 30	90 ± 28	0.66
Posterior wall thickness, cm	1.0 ± 0.2	0.9 ± 0.2	0.029
LV mean wall thickness, cm	1.0 ± 0.2	1.0 ± 0.2	0.31
LV function			
LVEF, %	59 ± 9	59 ± 10	0.21
LV GLS, % (2ch)	-16.1 ± 3.4	-16.1 ± 3.3	0.84
E wave, cm/s	92 ± 28	87 ± 28	0.007
A wave cm/s	74 ± 27	74 ± 25	0.71
E/A ratio	1.4 ± 0.8	1.3 ± 0.7	0.06
TDI septal a', cm/s	6.4 ± 2.2	6.7 ± 2.0	0.06
TDI septal e', cm/s	5.8 ± 1.8	5.8 ± 1.8	0.75
Left atrial size and function			
LA diameter, cm	4.2 ± 0.7	4.3 ± 0.6	0.046

LA area, cm2	22.9 ± 5.8	23.1 ± 5.4	0.6
LA volume, ml	74 ± 32	76 ± 27	0.42
LA volume index, ml/m2	35 ± 20	40± 15	0.92
TR velocity, m/s	2.7 ± 0.5	2.6 ± 0.4	0.22
Pulmonary pressures and right ventricle			
PASP, mmHg	35 ± 11	34 ± 10	0.21
TAPSE, cm	1.8 ± 0.4	1.8 ± 0.4	0.46
RVFAC, %	47.4 ± 9.2	45.2 ± 9.4	0.03
RVEDA, cm2	20.9 ± 5.8	21.8 ± 6.8	0.15
RVESA, cm2	11.1 ± 4.0	12.0 ± 4.7	0.027

Values are n, mean ± SD or median (interquartile range) unless otherwise specified. A'= peak late velocity; e'= peak early diastolic mitral annular tissue velocity; E wave = peak early diastolic trans mitral flow velocity; LVESD = left ventricular end-systolic dimension; FAC = fractional area change; LA = Left atrial; LV=left ventricular, LVEDD= left ventricular end-diastolic dimension; LVEDVi= left ventricular end-diastolic volume indexed to body surface area; LVESD = LV ventricular end-systolic dimension; LVESVi = left ventricular systolic volume indexed to body surface area; PASP = pulmonary artery systolic pressure; RVEDA = right ventricular end-diastolic area; RVESA = right ventricular end-systolic area; RWT = relative wall thickness; s' = peak systolic mitral annular tissue velocity; TAPSE = tricuspid annular plane systolic excursion; TDI = Tissue Doppler Imaging; TR = tricuspid regurgitation, other abbreviations as in table 1

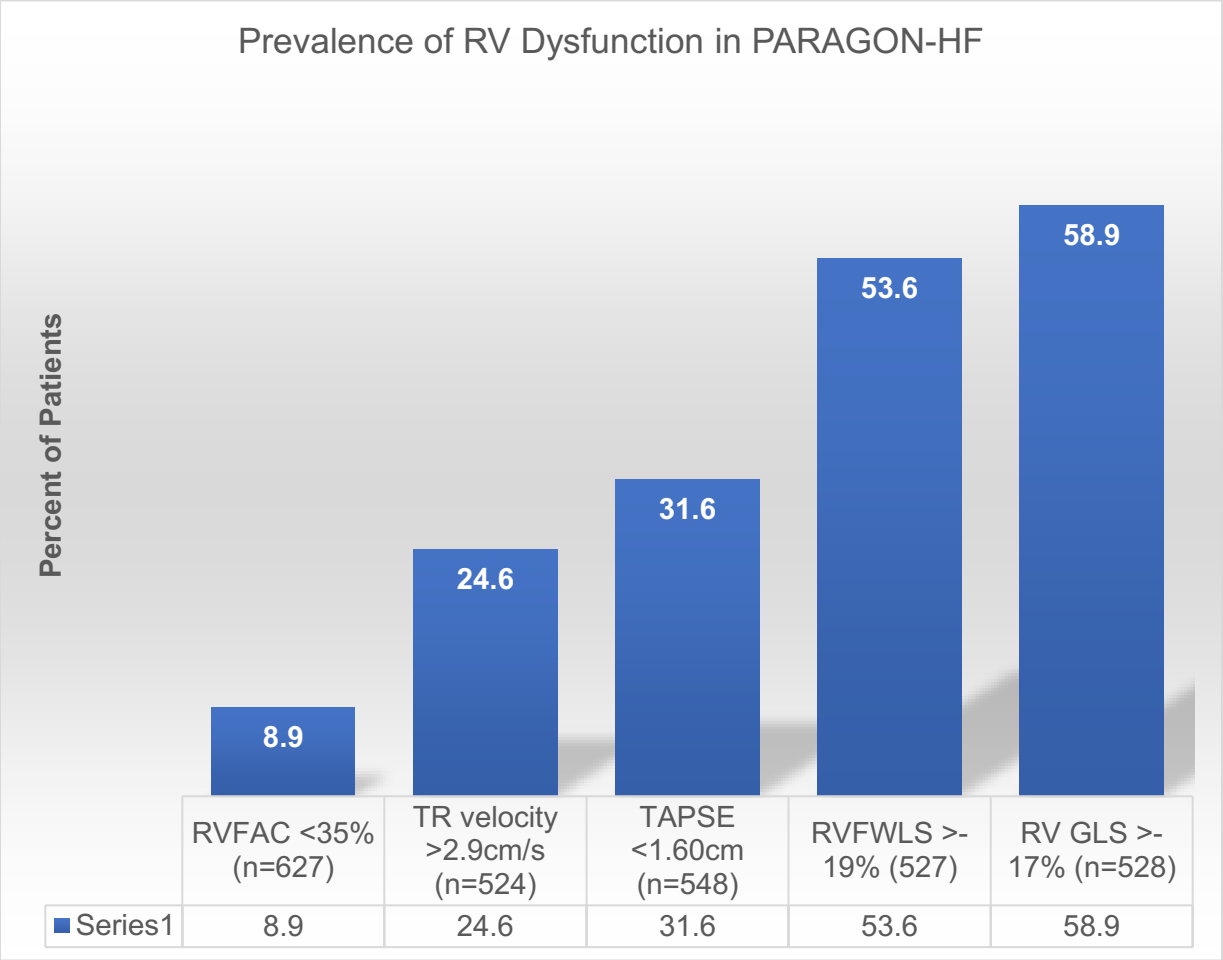


Figure 1.4: Prevalence of Right ventricular dysfunction per RV systolic function measurements

RV – Right ventricular; RVGLS – right ventricular global longitudinal strain; RVFWLS – right ventricular free wall longitudinal strain; TAPSE – tricuspid annular plane systolic excursion; TR velocity – tricuspid regurgitant peak jet velocity; RVFAC – right ventricular fractional area change.

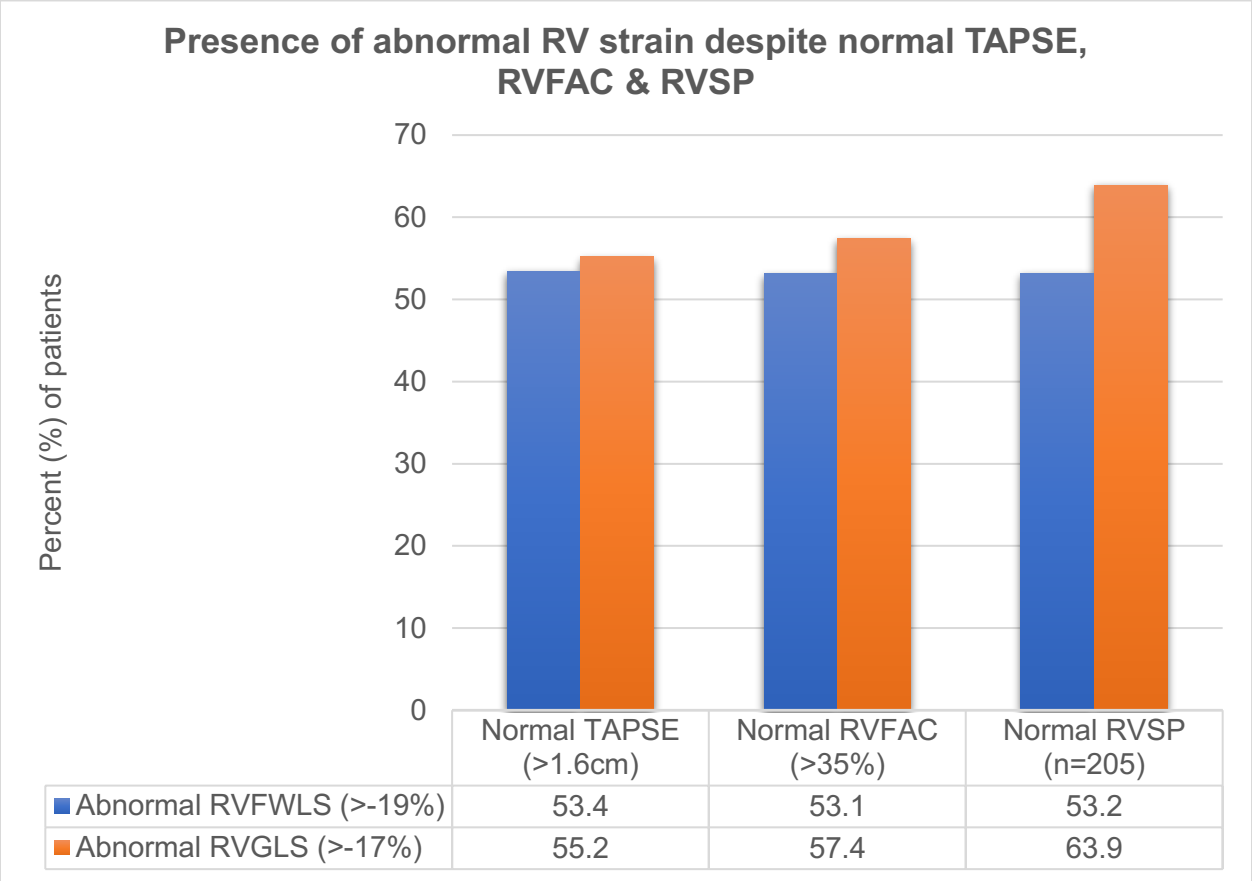


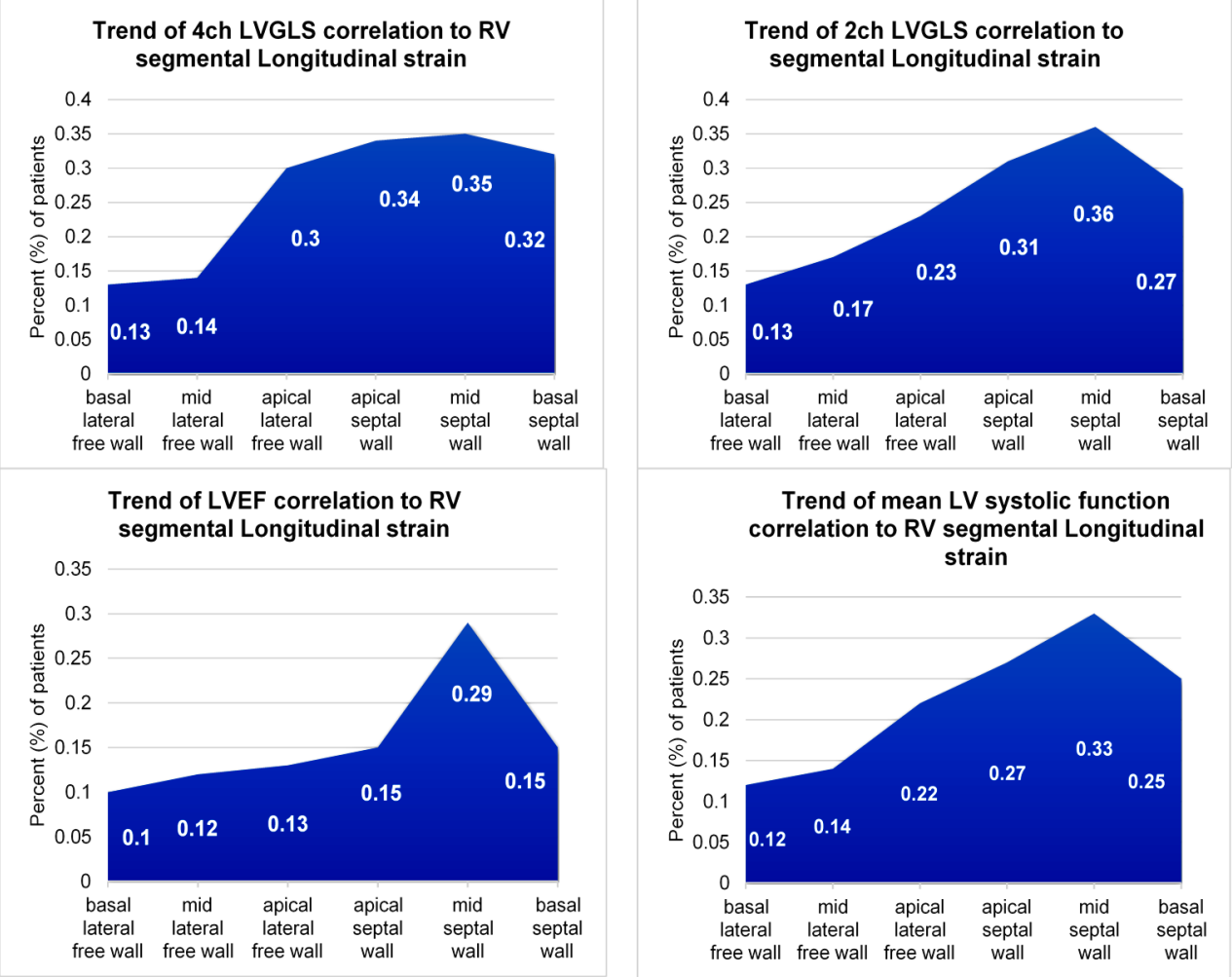
Figure 1.5: Bar chart illustrating prevalence of subclinical right ventricular dysfunction

RV – Right ventricular; RVGLS – right ventricular global longitudinal strain; RVFWLS – right ventricular free wall longitudinal strain; TAPSE – tricuspid annular plane systolic excursion; TR velocity – tricuspid regurgitant peak jet velocity; RVFAC – right ventricular fractional area change. *Subclinical right ventricular dysfunction (RVD; impaired or abnormal RV myocardial strain despite normal conventional systolic estimates). Abnormal RV systolic function reflected as impaired strain was present in at least half of patients with normal conventional measurements. Abnormalities were more frequent when estimated by RVGLS (red) compared to RVFWLS (blue)*

Table 1.3: Baseline, left ventricular and right ventricular systolic correlates of RVGLS and RVFWLS

		RVGLS		RV FWLS	
variable	N	r	p value	r	p value
Baseline correlates					
age	527	0.05	0.28	0.07	0.1
systolic BP	527	-0.03	0.4	-0.07	0.1
heart rate	527	0.14	0.002	0.15	<0.0001
BMI	527	0.09	0.05	0.13	0.004
Creatinine	527	0.06	0.19	0.14	0.002
GFR	524	0.02	0.7	-0.06	0.2
log NTproBNP	519	0.16	0.0003	0.2	<0.0001
LV systolic function correlates					
LVEF, %	527	-0.15	0.001	-0.14	0.001
A4C LVGLS, %	503	0.39	<0.0001	0.33	0.001
A2C LV GLS, %	392	0.39	<0.001	0.31	<0.0001
RV systolic function correlates					
RV ejection time	365	-0.18	<0.0001	-0.23	<0.001
RVEDA	527	0.07	0.09	0.09	0.04
RVESA	527	0.17	<0.001	0.23	<0.0001
RVFAC	527	-0.23	<0.0001	-0.31	<0.0001
RVMPI	233	0.16	0.02	0.17	0.01
RVOTVTI	363	-0.21	<0.0001	-0.19	<0.0001
TRV	282	-0.1	0.1	-0.05	0.42
TAPSE	297	-0.28	<0.001	-0.33	<0.001

A2C= Apical two-chamber, A4C = Apical two-chamber, BMI = Body mass index, LVEF = Left ventricular ejection fraction, LV = left ventricular, RV = Right ventricular, BP = Blood pressure GFR = Glomerular Filtration rate, LV GLS = Left ventricular global longitudinal strain, TAPSE= Tricuspid annular plane systolic excursion, TRV = Tricuspid regurgitant peak velocity, RVOTVTI = RV outflow tract velocity time index, RVFAC= RV fractional area change, RVEDA = right ventricular end-diastolic area, RVESA = Right ventricular end-systolic area, RVMPI – right ventricular index of myocardial performance



LVEF-Left ventricular ejection fraction; 4ch – apical-4-chamber view; 2ch – apical-2-chamber view; LVGLS - left ventricular global longitudinal strain

Figure 1.6: Area plot illustrating trends in correlation coefficient (R) of relationship between LV systolic measurements and segmental longitudinal strain in lateral free and septal walls of the right ventricle.

R coefficients of correlatin between LV systolic function and longitudinal strain peaks in septal wall segments (basal, mid, apical) and troughs in lateral free wall segments. LV systolic influence on RV decreases moving from septal wall to Trend was the same in individual or mean LV systolic R coefficients. LVEF (upper left), 4-Chamber LVGLS (lower left), 2-chamber LVGLS (upper right), mean LV systolic R coefficients (lower right)

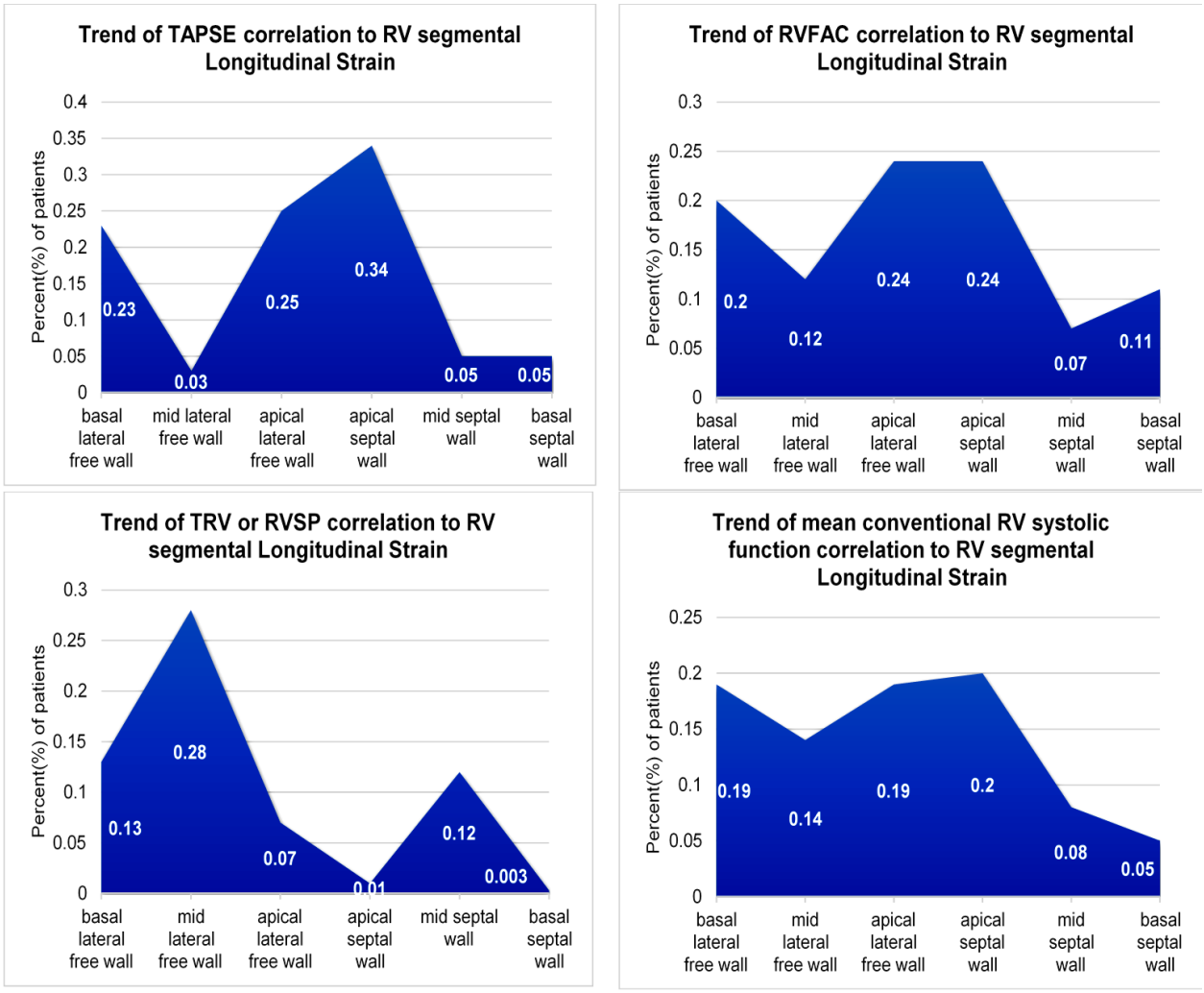


Figure 1.7: Area plot illustrating trends in correlation (R) coefficient of relationship between RV systolic measurements and segmental longitudinal strain in free and septal walls of the right ventricle

R coefficients of correlation between RV systolic function and RV segmental longitudinal systolic strain peaks in lateral free wall segments (basal, mid, apical) and troughs in septal wall segments. Trend was the same in individual or mean LV systolic R coefficients. LVEF (upper left), 4-Chamber LVGLS (lower left), 2-chamber LVGLS (upper right), mean LV systolic R coefficients (lower right)

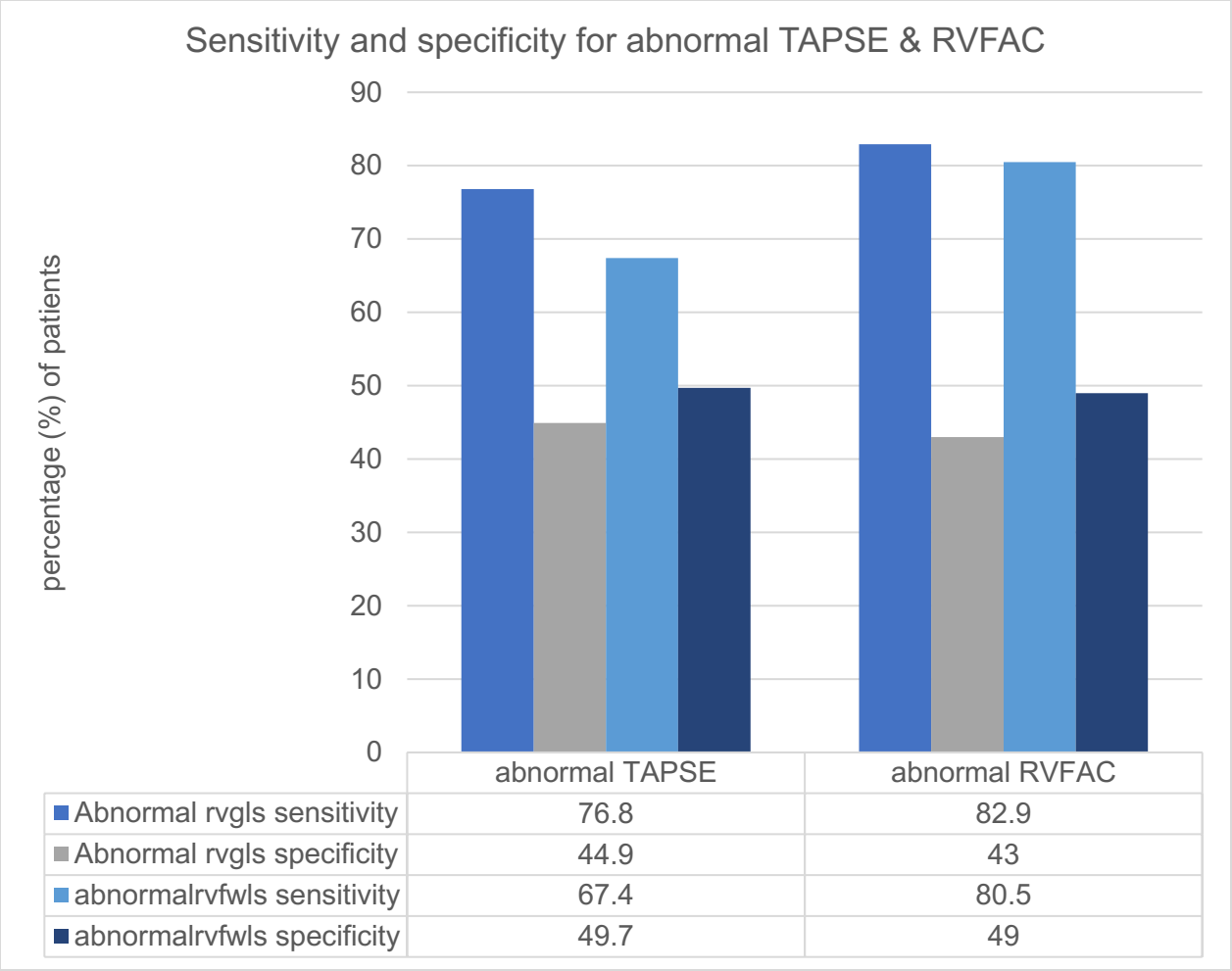


Figure 1.8: Bar charts with bars illustrating sensitivity and specificity of RVGLS and RVFWLS to detect abnormalities of RVFAC and TAPSE

RV systolic dysfunction; abnormal TAPSE (left) and RVFAC (right). RVGLS had very good sensitivity for both RVFAC and TAPSE which was higher compared to RVFWLS. Meanwhile RVFWLS had an acceptable specificity for abnormal RVFAC and TAPSE, which were higher compared to RVGLS

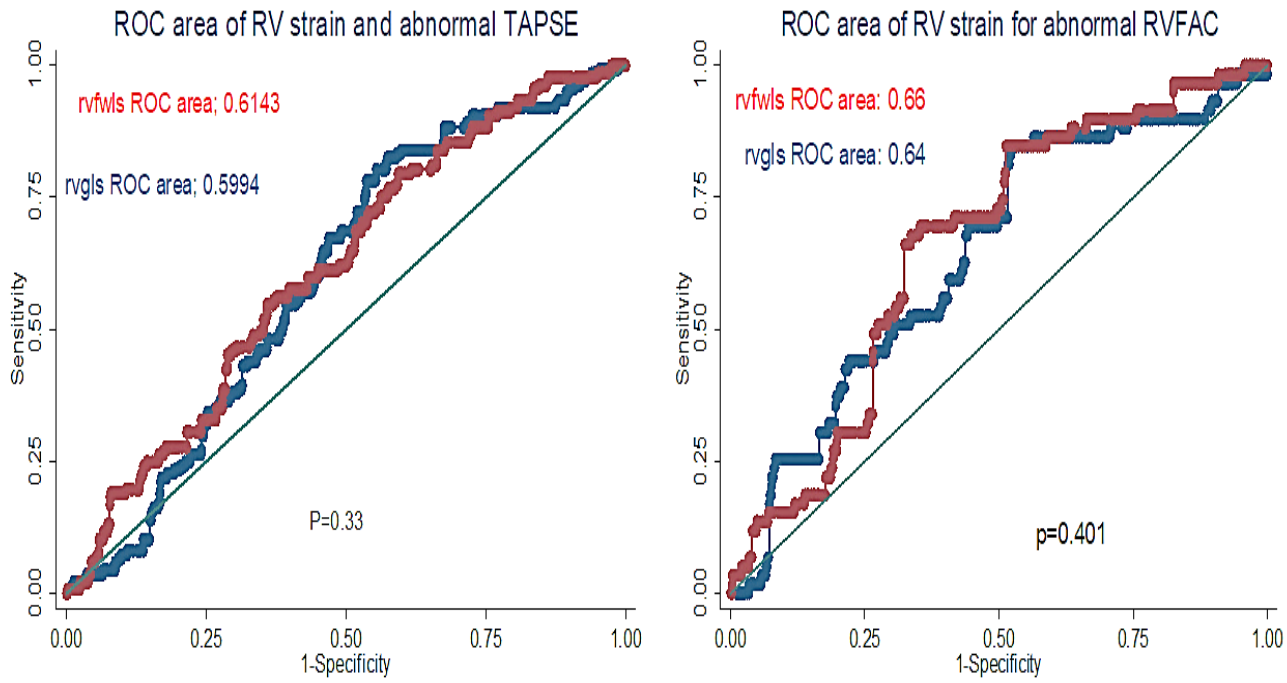


Figure 1.9: Comparison of receiver operating characteristic area under the curve (AUC) for RVFWLS to discriminate patients having abnormal TAPSE and RVFAC *(RVGLS AUC < RVFWLS AUC in stratifying patients to have abnormal conventional RV systolic function (abnormal TAPSE: left, abnormal RVFAC: right).*

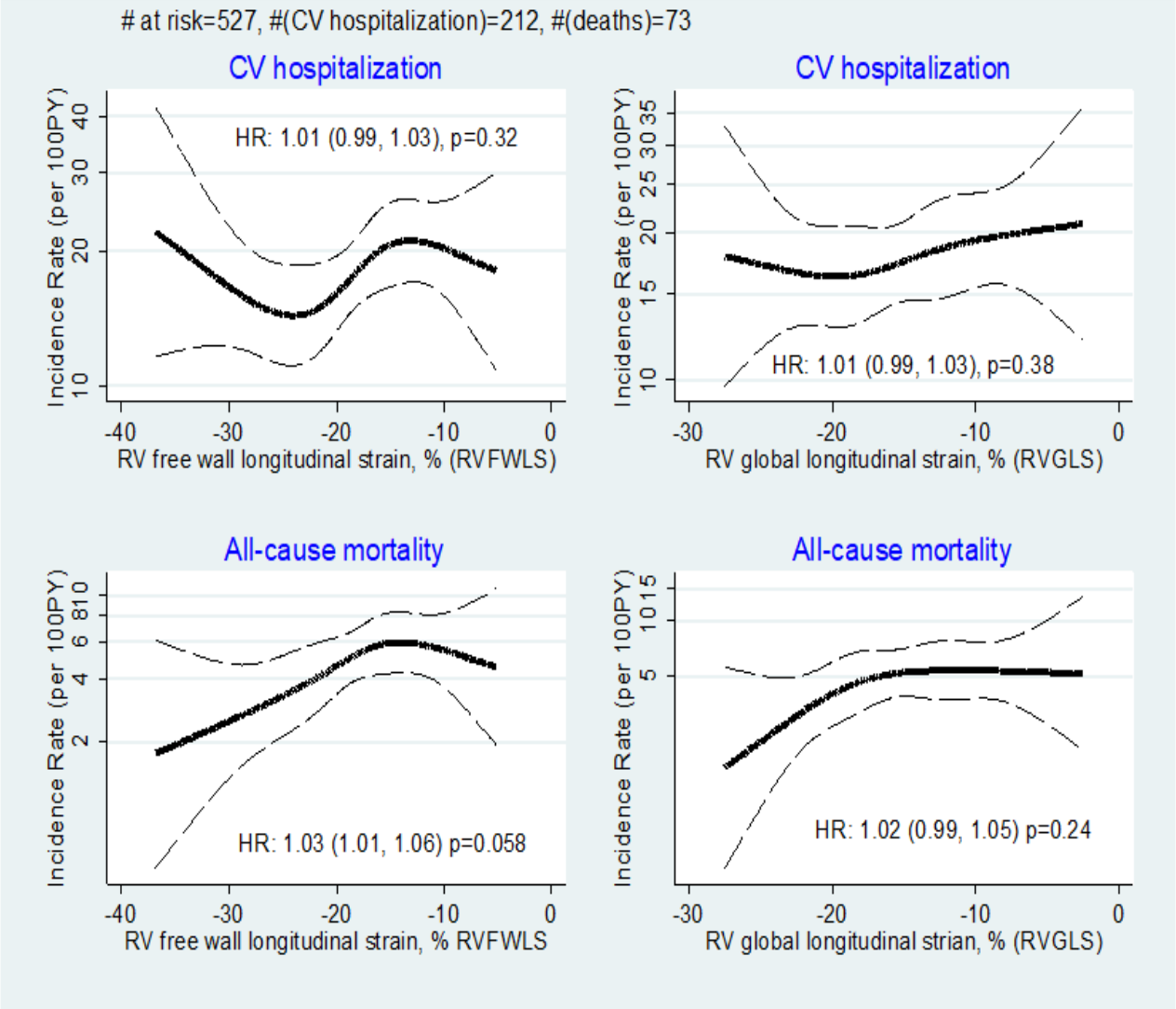


Figure 1.10: Restricted cubic spline plots illustrating association between outcome events and per 1% increase in RV myocardial strain

Crude incidence and risk of cardiovascular hospitalization and all-cause death per 1% increase in RV free wall longitudinal strain (RVFWLS: left) and RV global longitudinal strain (RVGLS: right)

Table 1.4: Event rate, # events, crude and adjusted hazard of exposure (RVGLS and RVFWLS) as either continuous or dichotomous variable for outcomes (cardiovascular hospitalization and all-cause mortality)

Variable	Events, IR	Cardiovascular Hospitalization (n=217)		All-cause deaths (n=73)	
RVGLS		Crude HR	Adjusted HR	Crude HR	Adjusted HR
Continuous	73	1.01 (0.99, 1.03), p=0.38	1.02 (0.98, 1.05), p=0.36	1.02 (0.99, 1.05) p=0.24	1.0 (0.95, 1.05), p=0.998
Normal (<-19%)	84, 16.5per 100PY	reference	reference	reference	reference
Abnormal (>-19%)	133 18.7 per 100PY	1.12 (0.85, 1.48), p=0.41	1.17 (0.79, 1.74) p=0.42	1.08 (0.75, 1.54), p=0.69	0.95 (0.56, 1.63), p=0.86
RVFWLS					
Continuous	217	1.01 (0.99, 1.03), p=0.32	1.01 (0.98, 1.05), p=0.35	1.03 (1.01, 1.06) p=0.058	1.03 (0.99, 1.08), p=0.14
Normal (<-19%)	90 15.7per 100 PY	Reference	reference	reference	reference
Abnormal (>-19%)	127 19.6 per 100PY	1.24 (0.95, 1.62), p=0.12	1.41 (0.95, 2.09), p=0.09	1.40 (0.97, 2.02) p=0.07	1.49 (0.84, 2.65), p = 0.17

HR – Hazard Ratio; Adjusted HR for age, sex and pulmonary pressures; IR- Incidence rate; RVFWLS – right ventricular free wall longitudinal strain; RVGLS – right ventricular global longitudinal strain

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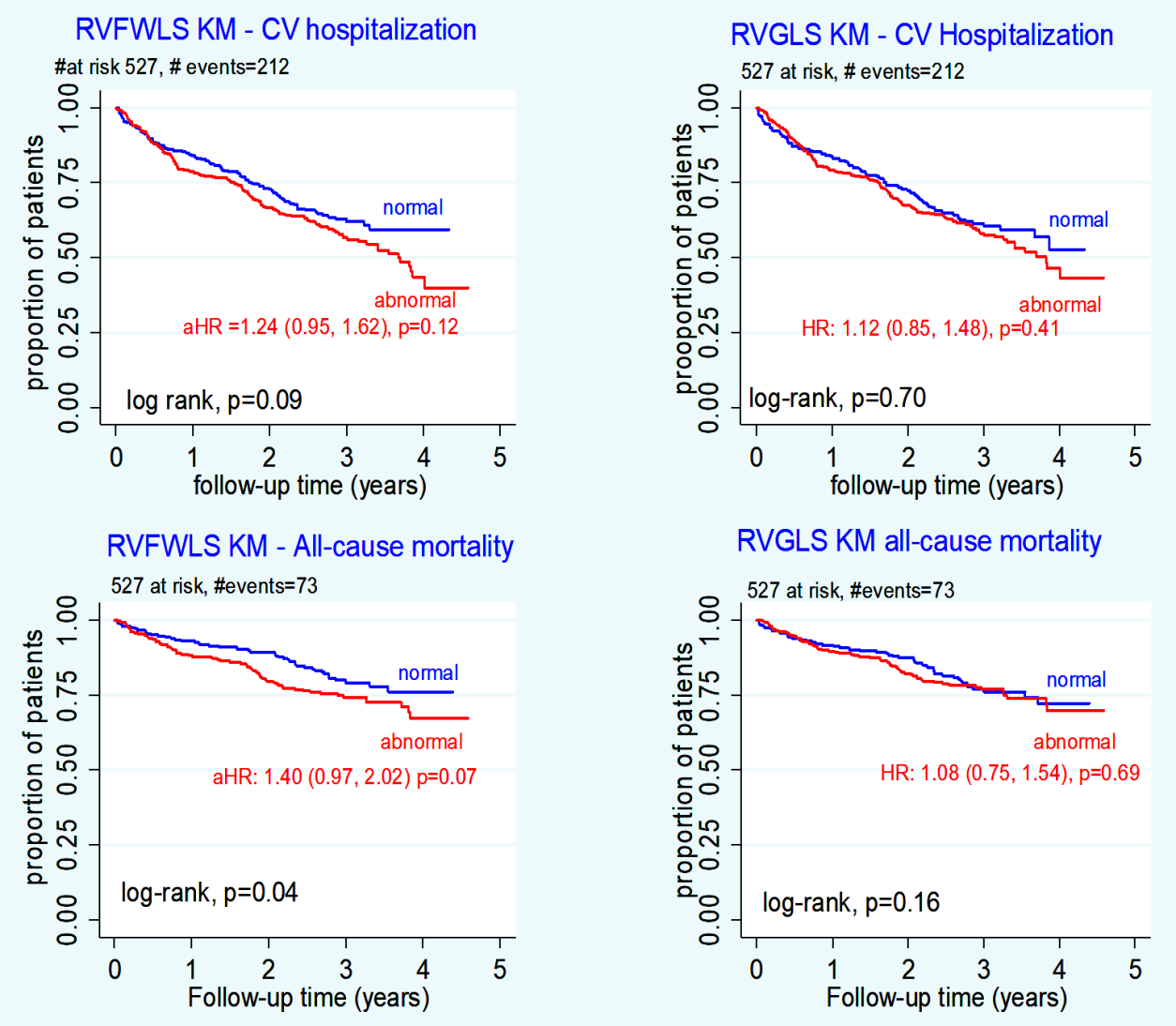

Figure 1.11: Kaplan Meier estimates and curves for cardiovascular hospitalization and all-cause mortality comparing normal to abnormal RVFWLS (left) and RVGLS (right)

Table 1.5: Supplementary table: Incidence of cardiovascular hospitalization and all-cause mortality by categories or abnormal RVGLS and RVFWLS

	RVGLS, n (%)			RVFWLS, n (%)		
	Normal	Abnormal	p value	Normal	Abnormal	p value
all-cause death	25 (11.6)	48 (15.4)	0.21	**25 (10.2)**	**48 (17.0)**	**0.024**
Cardiovascular hospitalization	84 (38.9)	133 (42.8)	0.37	**90 (36.7)**	**127 (45.0)**	**0.05**

Table 1.6: Supplementary table 2: Correlation of conventional RV systolic measurements with segmental longitudinal strain

Conventional RV systolic function correlates per RV regional segmental longitudinal strain					
	RV segment	RVFAC *R*	TAPSE *R*	TRV *R*	mean RV systolic R
RV lateral free wall	basal lateral free wall	0.2	0.23	0.13	0.19
	mid lateral free wall	0.12	0.03	0.28	0.14
	apical lateral free wall	0.24	0.25	0.07	0.19
RV septal wall	apical septal wall	0.24	0.34	0.01	0.2
	mid septal wall	0.07	0.05	0.12	0.08
	basal septal wall	0.11	0.05	0.003	0.05
Mean (RV free wall): mean (septal wall) ratio		1.33	1.16	3.61	1.58

RV – right ventricular; FAC – fractional area change; TAPSE – tricuspid annular plane systolic excursion; TRV – tricuspid peak jet regurgitant velocity

Table 1.7: Supplementary table 3: Correlation of left ventricular systolic measurements with segmental RV longitudinal strain

		LV systolic function correlation coefficients			
	RV wall segments	LVEF	2ch LV GLS	4ch LVGLS R	Mean LV systolic *R*
RV lateral free wall	basal lateral free wall	0.1	0.13	0.13	0.12
	mid lateral free wall	0.12	0.17	0.14	0.14
	apical lateral free wall	0.13	0.23	0.3	0.22
Septal free wall	apical septal wall	0.15	0.31	0.34	0.27
	mid septal wall	0.29	0.36	0.35	0.33
	basal septal wall	0.15	0.27	0.32	0.25
mean (free wall): septal ratio		0.51	0.56	0.56	0.56

RV – right ventricular; LVEF – left ventricular ejection fraction; 4ch – apical 4-chamber view; 2ch – apical – 2-chamber view; GLS – Global longitudinal strain

CHAPTER 2. Right ventricular free wall longitudinal strain and adverse outcomes in patients with HEFpEF; A secondary analysis of RV myocardial strain and primary composite outcome of PARAGON-HF trial

Right ventricular free wall longitudinal strain is independently associated with recurrent heart failure hospitalization and cardiovascular death in patients with Heart Failure preserved ejection fraction

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Abstract

Aim: To assess impaired right ventricular free wall longitudinal strain (RVFWLS) and its association to adverse outcomes in HFpEF

Background: The prognostic relevance of impaired right ventricular (RV) longitudinal systolic strain are less well described in heart failure preserved ejection fraction (HFpEF).

Methods: RVFWLS was assessed in 527 participants of the Prospective comparison of ARnI with Arb Global Outcomes in heart failure with preserved ejectioN fraction trial (PARAGON-HF). Participants with no cardiac images, missing RV focused views, poor quality images were excluded. Participants were categorized into RVFWLS tertiles (<-21.4, -21-4 to -16.0, >-15.9). Cox regression was used to associate RVFWLS to the primary composite endpoint of first, recurrent heart failure hospitalization or cardiovascular death.

Results: Overall mean was -18.95±6.82% and 311 (59%) had abnormal RVFWLS (>-20%). Male gender, diabetes, atrial fibrillation was significantly more prevalent in patients having RVFWLS >-15.9%. patient group with RVFWLS >-15.9% had a higher body mass index, heart rate, NTproBNP as well as lower left ventricular ejection fraction (LVEF). There was a crude linear trend of increase in events per 1% continuous increase in RVFWLS that persisted after adjusting for pulmonary pressures [aHR: 1.06 (1.0, 1.09), p=0.004] and baseline covariates [aHR: 1.05 (1.02, 1.09), p=0.02]. Trend was similar in apical and basal segments of the RV lateral free wall. Compared to the subgroup with normal RVFWLS (<-21%), the group with RVFWLS >-15.9% had a higher incidence rate and at least two-times the risk for primary endpoint after pulmonary pressures and baseline covariates [aHR: 2.19 (1.13, 4.2), p=0.020]

Conclusion: Abnormal RVFWLS is prevalent in HFpEF. RVFWLS was independently associated with recurrent HF hospitalization or cardiovascular death in HFpEF patients. This association is most likely driven by systolic abnormalities in apical and basal segments of the RV lateral free wall. RVFWLS may be useful in identifying HFpEF patients at high risk of adverse outcomes in clinical setting. Larger studies are needed to validate these findings

Keywords: Heart failure preserved ejection fraction, right ventricular myocardial strain, predictors, outcomes

Word count: 318

Key messages (highlights)

- RV systolic dysfunction (RVFWLS>-20%) is prevalent in HFpEF. More than half patients in this sub study of enrolled participants in PARAGON-HF were estimated to have abnormal RV free wall strain at baseline. This validates previous reports which have suggested that RV dysfunction may be underestimated by conventional RV echocardiographic assessments
- RV free wall longitudinal strain is an independent predictor of total (first or recurrent) heart failure hospitalizations or cardiovascular death in patients with HFpEF. Patients with RVFWLS in range <-15.9 had approximately more than two-times risk for recurrent heart failure hospitalizations or cardiovascular death compared to patients with normal RVFWLS (>21%). RVFWLS may be useful clinically in identifying HFpEF patients at high risk of adverse outcomes.

Word count: 6730

Introduction:

Heart failure with preserved ejection fraction (HFpEF) is associated with excess hospitalization and mortality (1-3). The prevalence of HFpEF appears to be on the rise(4), however; as yet there is no proven medical therapy for HFpEF (5, 6). Identifying patients with HFpEF at risk of adverse outcomes and aggressive therapy remains the best strategy to minimize adverse outcomes. Historically, the natural history of HFpEF has focused on the left heart whereas the right ventricle is less well described. Nevertheless, emerging evidence points to the right ventricle as an opportunity for further investigation and its role in HFpEF is gaining more attention.(7, 8).

Right ventricular dysfunction has been recognized as prevalent in HFpEF and is associated with adverse outcomes in HFpEF. (7-12). Nevertheless, most of the published studies have utilized conventional echocardiography which has known limitations.(7, 13, 14). RV myocardial deformation imaging has been shown to be a feasible, reproducible and effective means to assess RV function(13, 15-17). Additionally, RVFWLS has the advantage of being less susceptible to load-/angle dependency and tethering of imaging which are known limitations of conventional RV echocardiographic assessment. (7, 18, 19).

Although RV deformation imaging is recommended for assessment of RV(18), it is not used routinely in clinical practice. There are limited reports on the prognostic relevance of RVFWLS in HFpEF. Thus, we aimed to investigate the RVFWLS and its association to the primary composite endpoint (first, recurrent hospitalization for heart failure or cardiovascular death) in participants enrolled in PARAGON-HF (Prospective comparison of ARnI with Arb Global Outcomes in heart failure with preserved ejectioN fraction).

Methods

Study population

PARAGON-HF was a multicenter, international, randomized double-blind, event-driven trial

testing the long-term efficacy and safety of sacubitril-valsartan compared with valsartan alone in adult patients with signs and symptoms with HF and LVEF ≥45%. Inclusion criteria and results have been previously described in detail(ref). Briefly, PARAGON HF enrolled 4,822 patients at 752 sites in 43 countries who were ≥ 50 years of age, and who met the following criteria: LVEF ≥45%, current symptomatic HF requiring diuretics for ≥ 30 days (NYHA II – IV), structural heart disease and an elevated NT-proBNP (6, 20).

Echocardiography

Baseline echocardiograms for each participant were obtained by site investigators according to the study-specific protocol. Echocardiograms were sent in digital format to the core laboratory, where quantitative measures were performed in accordance with the American Society of Echocardiography (ASE) guidelines, by dedicated analysts blinded to clinical information and randomized treatment assignment. Each measure was performed by the same analyst for all study participants. Echocardiographic features of PARAGON participants as well as Intra observer and interobserver variability have been previously published(20, 21). A total of 1087 PARAGON HF participants had cardiac imaging. Patients with insufficient echocardiographic quality were excluded from analyses

Strain analyses

Strain analyses were performed offline at the Cardiac Imaging Core Lab, Brigham and Women's Hospital, Boston. All available echocardiograms were screened for RV myocardial strain. Global and regional longitudinal RV strain and strain rate were assessed in the apical four-chamber view focused on RV. Only echocardiograms having an apical four-chamber view focused on RV or with clear RV walls were included in strain analysis. A semiautomated speckle tracking software (TOMTEC Imaging Systems Image-Arena v4.6 build 4.6.3.9, Unterschleissheim, Germany) was used to assess RV myocardial deformation: this method has been reported to have excellent reproducibility in our laboratory and in our present study population(20).

After identification of the one cardiac cycle (R-R interval based on QRS waveform) on the simultaneous electrocardiogram, semiautomated tracing of the RV endocardial border in basal, mid and apical regions of both RV free and septal wall (Figure 2.1). Global RV free wall and septal peak longitudinal scores were calculated from the mean of the three free wall regions and the three septal regions, respectively. The tracking of each region was carefully inspected and manually adjusted if needed. If >2 segments could not be tracked, the measurements were considered unreliable and the echocardiogram was excluded from the analysis. All echocardiograms were screened, and tracings were performed by a single investigator blinded to treatment assignment, clinical/demographical data, and clinical outcomes.

Reproducibility and reliability

One of the authors conducted all the RV myocardial strain analyses offline at the Cardiac Imaging Core Lab (CICL). Investigator was trained to perform two-dimensional echocardiography and speckle tracking imaging till satisfactory standards of the CICL. Reproducibility of baseline conventional echocardiograph analyses at the CICL has been previously reported. For the R RV myocardial strain analyses, investigator's reproducibility was assessed and reported in 60 echocardiograms (Table 2.7).

Statistical Analysis

Continuous data are expressed as mean ± standard deviation (SD). Categorical data are presented as frequencies and percentages. Abnormal RVFWLS was defined as a peak absolute value of <20% in accordance with American Society of Echocardiography guidelines(18). Baseline clinical, laboratory and echocardiographic characteristics were stratified by sub groups according to tertiles of RVFWLS (<-21.4, -21.4 to -15.9, >-15.9%). Spearman's correlation was used to test relationship between RVFWLS to log-transformed NTproBNP and left ventricular ejection fraction (LVEF). The primary outcome of PARAGON-HF was the composite of first, recurrent HF hospitalizations and cardiovascular death after follow-up(6, 20). Unadjusted, RV

afterload adjusted, and multivariable-adjusted cox proportional regression analyses stratified by region were performed to determine association to individual outcome events while semiparametric proportional rates method of Lin et al, as per the PARAGON-HF paper were used to analyze associations to primary composite, total (first + recurrent) heart failure hospitalization and cardiovascular deaths. Associations were tested either as continuous RVFWLS or by tertile subgroups of RVFWLS. All statistical tests were two-sided. Restricted cubic splines with 4 knots were used to illustrate associations of trends per 1% continuous increase of RVFWLS to incidence of primary composite or individual outcome events. Cumulative hazard estimates and curves were plotted for primary composite and individual component outcomes for RVFWLS tertile subgroups. P value of <0.05 was considered statistically significant for all tests. Data were analyzed using Stata/SE 14.2 (StataCorp, TX)

Results

Of 4822 participants who met PARAGON HF inclusion criteria, 3827 were excluded for no available cardiac images. Of 1087 with available 2D echocardiograms, 220 were not in DICOM format and 281 had missing RV focused views. Of 586 with RV focused apical 4-chamber views, RV endocardial border was unreliable in 59 who had 2 or more missing regions on RV free wall. A total of 527 echocardiograms with measured RV longitudinal strain were included in these analyses. (Figure 2.2)

Of 527, 311 (59%) had abnormal RVFWLS (<-20%) (Figure 2.3). The mean RVFWLS was -18.95 ± 6.82%. Patient group with RV strain analyses, compared to groups having cardiac imaging but no RV strain and group without cardiac imaging were; slightly older, had different distribution by region and significantly lower proportion of whites, comorbidities (ischemic heart disease, diabetes, hypertension) with lower estimates of body mass index, systolic blood pressure and heart rate. Also, there were similarities in age, dyspnea, NT-proBNP comparing group with RV

strain analyses to groups with cardiac imaging having no strain analyses and group without cardiac imaging (Table 2.4).

Most of the baseline echocardiographic characteristics were similar but for significantly lower LV end-diastolic volume and higher mitral valve late diastolic A wave in group with RV strain compared to groups having cardiac imaging with no RV strain and group without cardiac images (Table 2.5)

Baseline characteristics

Table 2.1 reports the baseline characteristics of PARAGON-HF participants according to subgroups of RVFWLS. The 3 groups had similar age, proportion of ischemic heart disease, hypertension, stroke, prior heart failure hospitalization, myocardial infarction, dyspnea and similar use of heart failure medication. Diabetes, atrial fibrillation and regional differences were more frequent while female gender was less frequent in groups with lower RVFWLS. Mean body mass index and heart rate were higher in groups with RVFWLS >-15.9%. Laboratory markers, N-terminal pro-brain natriuretic peptide (NT-proBNP) and creatinine where higher in group of patients with lower RVFWLS (>-15.9%). Patient group with RVFWLS >-15.9% also had lower mean ejection fraction at screening compared to other groups (Table 2.1)

Baseline Echocardiographic characteristics

Table 2.2 reports echocardiographic and Doppler characteristics stratified by subgroups of RVFWLS. Compared to group with normal RVFWLS (<-21.4%), patients with RVFWLS in range of -21.4 to -15.9% and RVFWLS>-15.9% had significantly higher LV end-systolic diameter, left ventricular end-systolic volume, septal wall thickness, LV mass index, posterior wall thickness and right ventricular end-systolic area. Patients in Tertile 2 and 3 had lower left ventricular ejection fraction, LV global longitudinal strain, LV early (E) diastolic wave, TAPSE (Tricuspid Annular Plane Systolic Excursion), RVFAC (right ventricular fractional area change). Pulmonary pressures were similar in all 3 tertiles.

RVFWLS and primary outcome in PARAGON HF

Figure 2.5 shows the adjusted incidence rates of primary outcome, first or recurrent heart failure hospitalization and cardiovascular death per 1% increase in RVFWLS range of values. This trend Table 2.3 reports the incidence of each of the same endpoints for each subgroup of RVFWLS tertile. There was a linear trend for increase in crude incidence rate of the primary endpoint with per 1% continuous increase in RVFWLS, which persisted after adjusting for right ventricular afterload or pulmonary pressures. This observation further persisted after multivariable adjustment for baseline covariates. This trend was similar for all individual primary outcome component events with continuous decrease in RVFWLS. The incidence of primary composite endpoint was highest in the group of patients having RVFWLS >15.9% or more. The crude risk of primary outcome was approximately two times higher in the patient group with RVFWLS > -15.9% compared to the group with normal RVFWLS (< -21%) which persisted after adjusting for right ventricular systolic afterload pressures, baseline, clinical and echocardiographic covariates. The trends in incidence and risk for individual component events (first heart failure hospitalization or CV death) were similarly increasing with every 1% increase in RVFWLS (Figure 2.5). Incidence and risk of adverse outcomes increase across groups as range of RVFWLS. Patient groups with RVFWLS >-15.9% had the highest incidence and risk for outcome events (Table 2.3). However, the crude and adjusted risk of CV death in group having RVFWLS in range 15.9-21.3% was significantly higher (Table 2.3). Overall, the patient group that exhibited a RVFWLS >-15.9% presented with at least a two-times higher incidence rate and risk of requiring recurrent heart failure hospitalizations or cardiovascular death compared to the patient group with a normal RVFWLS (<-21%). A similar incidence and risk are observed in other outcomes including all-cause deaths and/or first hospitalization (Table 2.6)

Discussion

In 527 patients with HFpEF enrolled in PARAGON-HF, we found more than half the study cohort

had abnormal RVFWLS. We observed some differences in baseline characteristics based on RV free wall longitudinal strain tertile sub groups (<15.9, 16-21.4, >21.4%). RVFWLS correlated modestly with NTproBNP and left ventricular ejection fraction. Accounting for RV afterload (pulmonary pressure), baseline covariates (gender, atrial fibrillation, diabetes, prior history of heart failure hospitalization, heart rate, body mass index, log transformed NT-proBNP, LVEF), incidence and risk of primary recurrent events was associated with a unit increase in RVFWLS. Patients with RVFWLS <15.9% were more likely to experience a primary endpoint (first or recurrent heart failure hospitalization, or cardiovascular death), most probably due to an increased risk of heart failure hospitalization (Figure 2.5) and systolic function in basal and apical segments of the free wall (Figure 2.7). Overall, these findings suggest right ventricular dysfunction is highly prevalent in HFpEF; parallels left ventricular dysfunction but is independently associated with adverse outcomes in HFpEF.

Abnormal RV free wall longitudinal strain in HFpEF

RV dysfunction is defined as an abnormal estimate of a measure of right ventricular function. RV dysfunction is prevalent in HFpEF; however, the exact prevalence varies (7, 12). Using American society of Echocardiography recommended cut-offs for RV myocardial strain, we observed RV dysfunction in more than half of HFpEF participants (figure 4). Using conventional echocardiographic assessment, PARAGON-HF investigators have previously reported about one-third of patients had RV dysfunction (20). This discordance may be because pulmonary hypertension a load-dependent association of right ventricular function was also frequent in about a third of PARAGON-HF participants(20). Conventional echocardiographic RV estimates have inherent limitation of load-dependence and thus, may have inaccurately estimated RV as suggested in many reports(7, 15, 18, 19, 22). Also, our findings differed from Morris *et al*,(16) who found abnormal RVFWLS in about 12% of HFpEF patients. Also, Morris *et al* had lower estimates of abnormal conventional RV echocardiographic estimates in HFpEF compared to

baseline conventional RV abnormalities (16, 20).This may be because Morris *et al* defined abnormal RVFWLS as >-19% (16) while we defined abnormal RVFWLS was >-20% in accordance with ASE guidelines(14). Our findings are in accordance with findings in systematic reviews and meta-analyses which suggests RV dysfunction is potentially present in about half of the patients exhibiting HFpEF (7, 19). This further suggests the presence of subtle RV myocardial or subclinical RV changes in HFpEF which may be under- or inaccurately estimated by conventional measures.

Concomitant left and right-sided dysfunction

NT-proBNP and left ventricular ejection fraction are surrogates of left ventricular systolic function and have been shown to be predictors of adverse events in previous HFpEF trials(16, 20, 23, 24). We observed a modest linear relationship between baseline RV myocardial deformation with NT-proBNP and left ventricular ejection fraction (Figure 2.4). Also, groups with lower RVFWLS had higher NTproBNP and lower ejection fractions compared to groups with normal RVFWLS. These findings are consistent with several previous studies reporting the inter-relationship between worsening longitudinal systolic function of LV and RV(8, 22, 25). In a multicenter study, D.A Morris et al.(16) reported that RV free wall and global strain did correlate significantly with left ventricular ejection fraction in HFrEF but not in HFpEF. One possible explanation may be the difference in LVEF threshold for HFpEF. PARAGON-HF defined HFpEF as LVEF >45% while Morris et al. defined HFpEF as >50%. Scott et al, have suggested that patients with lower range LVEF may behave like those with HFrEF than with higher ejection fraction (24). The interdependence of the right ventricle on left ventricle is well known especially in HF with reduced ejection fraction and pulmonary hypertension(7, 19). However, the extent of this relationship is unclear in HFpEF. Nevertheless, it is apparent that RV dysfunction parallels LV dysfunction even in the absence of pulmonary hypertension.

Right ventricular free wall strain as a predictor of adverse events in HFpEF

There is increasing evidence on the natural history of right ventricle in HFpEF and its role in HFpEF. Load – dependent and – independent underlying mechanisms have been suggested to contribute to RV dysfunction(7). Pulmonary hypertension (high right ventricular afterload) is frequent in HFpEF, and an independent predictor of RV dysfunction and adverse outcomes in HFpEF (7, 12, 19, 20). We found there was a linear crude increase in incidence of primary endpoint for every 1% increase in RVFWLS, which persisted after accounting for pulmonary pressures and baseline, clinical and echocardiographic covariates. This trend of increasing incidence was similar but less marked in basal segment of the RV free wall (Figure 2.7). TAPSE is a measure of longitudinal displacement of basal segment of RV lateral wall and has prognostic value in HFpEF. The increasing trend of incidence of primary endpoint per increase in longitudinal strain was similarly observed in apical segment of the RV (Figure 2.7). This suggests that beyond abnormalities of basal segment; apical abnormalities of the free wall may also drive the association between RVFWLS and adverse outcomes in HFpEF. Additionally, patients with RVFWLS >-15.9% demonstrated independently higher incidence and risk of total hospitalizations or CV death compared to patients exhibiting normal RVFWLS (<-21.4%) (Figure 2.6). Numerous studies have also shown that impaired RV strain has prognostic relevance in heart failure reduced ejection fraction and other conditions(17, 19, 22, 26, 27). Our findings are similar to Lejeune et al(28) who similarly found impaired RV global strain (>-17.5%) to be independently associated with about two-times the risk for all-cause death or first heart failure hospitalization in patients with HFpEF. Our findings are also consistent with several studies reporting that abnormal individual RV echocardiographic systolic abnormalities are independently associated with adverse outcomes (7-10, 19, 22, 25). Based on these, we considered increasing RV free wall longitudinal systolic strain be an important predictor of increased risk for adverse outcomes in HFpEF.

Limitations

Despite our study findings, some limitations should be considered. Cardiac imaging was obtained from different site investigators using different imaging modalities. To mitigate risk of bias and Type 1 error, only one software system (TOMTEC) and only one of the authors conducted all the RV myocardial strain analyses. Reproducibility and repeatability of trained investigator compared to standards of the Cardiac Imaging Core Lab (CICL) are found in Table 2.7. Right ventricular function was assessed by right ventricular free wall strain whereas the gold standard for RV functional assessment is cardiac magnetic resonance imaging. Optimal cardiac imaging was not available in many patients. RV myocardial strain was feasible only in about 10% of all patients enrolled in PARAGON HF and about half of patients with available echocardiographic imaging. This limited our power to test associations especially in multivariable analyses of individual endpoints. Nevertheless, our cohort of 527 participants in HFpEF represents a relatively large sample of RV deformation imaging in HFpEF. Historically, there are limited RV studies with sample sizes that exceed 300 participants, and even more scarce in HFpEF trials. Like all other secondary analyses, our findings are hypothesis-generating and generalizability of these findings should be interpreted with caution as our cohort was a sub study of trial participants who met very strict inclusion criteria. Marked differences in participant characteristics were observed in those who had feasible strain compared to those who did not have strain measurements, and this may confound our analyses. We also only present association of outcomes to baseline strain and not serial measurements over time, hence, we could not exclude the presence of residual bias which may further confound our findings. Nevertheless, we accounted for observed differences in baseline characteristics associated with sub groups of RVFWLS. , The insights from our study findings remain valuable in our understanding of right ventricular dysfunction and its prognostic role in HFpEF.

Conclusions

In a subgroup of participants with HFpEF enrolled in PARAGON-HF, abnormal right ventricular longitudinal strain is highly prevalent. RV strain correlates modestly with LVEF and NtproBNP which are well established markers of LV systolic dysfunction and adverse risk in patients with HFpEF. We also observed that increasing RV free wall longitudinal strain was associated with increased risk of first or recurrent HF hospitalization or CV death, as well as CV death alone. This association seems to be driven by abnormalities or changes in apical and basal segment of the free wall. Thus, we suggest that RVFWLS strain may be used routinely in the clinical setting to identify HFpEF patients at high risk of developing adverse outcomes. Nevertheless, further prospective studies are needed to assess the clinical value and characterization of RV regional and segmental longitudinal strain in HFpEF. Further clinical trials or larger cohorts are needed to determine if clinical decisions based on RV myocardial strain imaging result in better patient outcomes.

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Disclosures: None

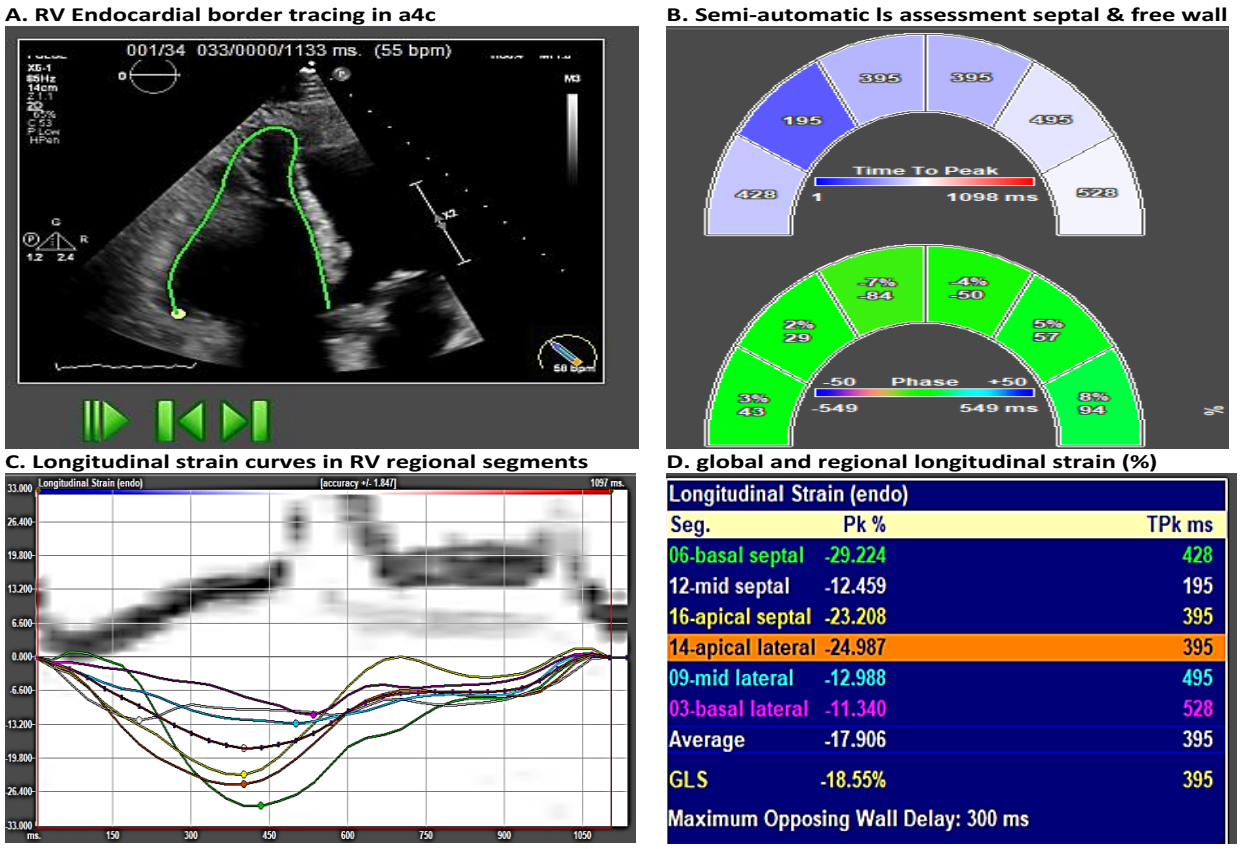

Figure 2.1: Illustration of right ventricular global systolic longitudinal strain in focused RV apical-four-chamber view in a PARAGON-HF participant using TOMTEC Image-Arena. A. Tracing endocardial border (upper left); B. Semiautomatic strain analyses (upper right): C. (peak strain curves or loops for each RV wall segment (lower left) D. Computed peak longitudinal strain in RV wall segments (*RVFWLS= mean peak longitudinal strain in 14-apical lateral, 09-mid lateral and 03-basal lateral RV free wall)*

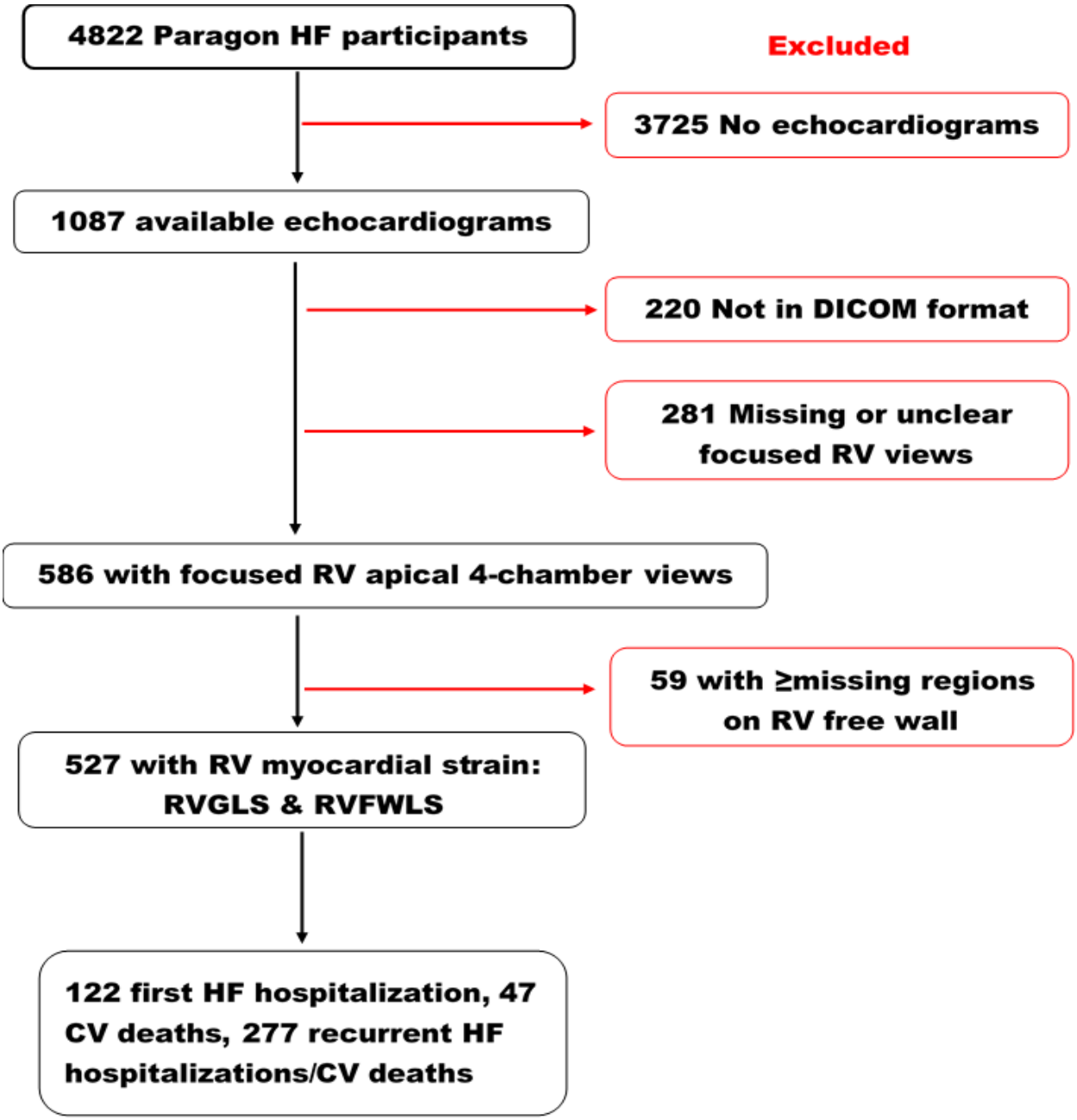

Figure 2.2: Consort flow chart for those included and excluded from our study analyses and primary endpoint; total (277; first + recurrent heart failure hospitalization and cardiovascular deaths) And individual component endpoints: first heart failure hospitalization (122) or cardiovascular death, Cardiovascular deaths ()

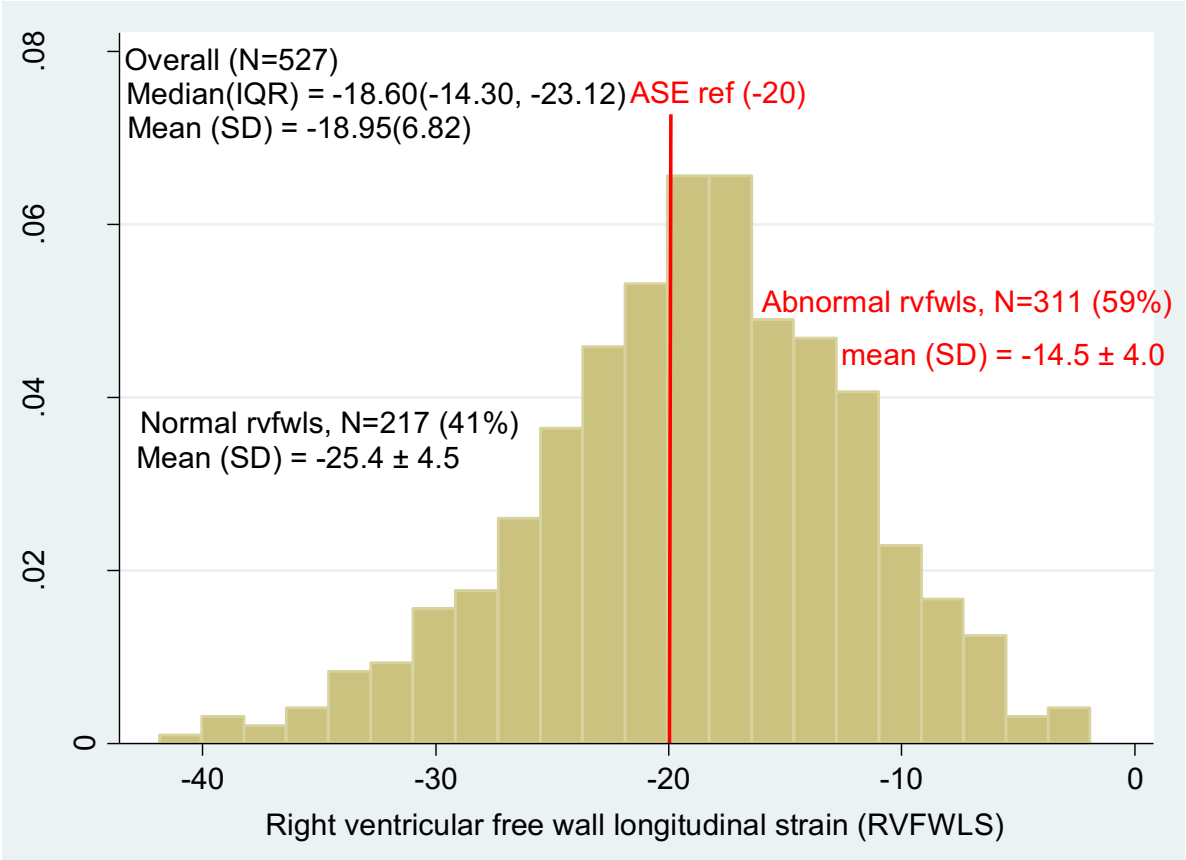

Figure 2.3: Histogram of right ventricular free wall longitudinal strain (RVFWLS).

Reference line for abnormal threshold at -20% in accordance with American Society of Echocardiography guidelines. Of 527 with RV myocardial strain, 311(59%) had abnormal RVFWLS values

Table 2.1: Baseline characteristics stratified by RVFWLS tertiles

variables	RV Free wall longitudinal strain, % (RVFWLS)			P Value
	RFWLS <- 21.4	-21.4<RVFWLS<- 15.9	RVFWLS >- 15.9	
	N=176	N=176	N=176	
Age, Years (Mean ± SD)	73.3 ± 7.9	74.8 ± 8.0	74.8 ± 7.8	0.12
Female, N (%)	115 (65.3%)	91 (52.0%)	92 (52.3%)	0.016
Race, N (%)				0.28
ASIAN	20 (11.4%)	35 (20.0%)	27 (15.3%)	
Black or African Americans	6 (3.4 %)	8 (4.6 %)	8 (4.5 %)	
OTHER	2 (1.1 %)	0 (0.0 %)	2 (1.1 %)	
WHITE	148 (84.1%)	132 (75.4%)	139 (79.0%)	
Region				0.002
Asia/Pacific And Others	27 (15.3%)	43 (24.6%)	25 (14.2%)	
Central Europe	45 (25.6%)	32 (18.3%)	22 (12.5%)	
Latin America	1 (0.6 %)	0 (0.0 %)	1 (0.6 %)	
North America	56 (31.8%)	52 (29.7%)	84 (47.7%)	
Western Europe	47 (26.7%)	48 (27.4%)	44 (25.0%)	
Ischemic Heart Disease, N (%)	43 (24.4%)	57 (32.6%)	52 (29.5%)	0.24
Diabetes, N (%)	51 (29.0%)	70 (40.0%)	70 (39.8%)	0.049
Hypertension, N (%)	162 (92.0%)	162 (92.6%)	167 (94.9%)	0.53
Stroke, N (%)	15 (8.6 %)	22 (12.6%)	22 (12.7%)	0.38
Prior HF Hospitalization	79 (44.9%)	83 (47.4%)	97 (55.1%)	0.14
History Of MI, n (%)	37 (21.0%)	35 (20.0%)	35 (19.9%)	0.96

NYHA, N (%)				0.85
2	129 (73.3%)	124 (70.9%)	130 (73.9%)	
3	46 (26.1%)	50 (28.6%)	46 (26.1%)	
4	1 (0.6 %)	1 (0.6 %)	0 (0.0 %)	
Body mass index, kg/m2	28.7 ± 4.6	29.1 ± 4.6	30.2 ± 5.4	0.01
Systolic BP, mm Hg	130 ± 17	126.8 ± 14.5	127.9 ± 17.1	0.18
Heart Rate, Bpm, Mean ± SD	67 ± 13	70 ± 12	71 ± 12	0.002
Creatinine, mmol/L (Mean ± SD)	96.6 ± 24.3	103.3 ± 33.1	103.9 ± 29	0.029
NT-ProBNP	1130.0 ± 1400.6	1296.9 ± 1210.1	1515.6 ± 1418.8	0.029
Ejection Fraction from Site	59.8 ± 7.6	58.5 ± 7.8	57.8 ± 6.9	0.033

BP- Blood Pressure; HF- Heart Failure, MI – Myocardial infarction; NT-ProBNP – N Terminal Pro Brain Natriuretic Peptide

Table 2.2: Baseline echocardiographic features stratified by RVFWLS tertiles

	RV free wall longitudinal strain (RVFWLS), %			
	RFWLS <-21.4	- 21.4<RVFWLS<-15.9	RVFWLS >-15.9	P value
LV structure				
LVEDD, cm	4.5 ± 0.7	4.5 ± 0.6	4.6 ± 0.7	0.52
LVEDV, cm3	99 ± 35	100 ± 30	104 ± 46	0.4
LVESV, cm3	39 ± 19	42 ± 19	47 ± 27	0.003
LVEDD, cm	4.5 ± 0.7	4.5 ± 0.6	4.6 ± 0.7	0.52
LVESD, cm	3.1 ± 0.7	3.2 ± 0.7	3.4 ± 0.7	0.025
Septal wall thickness, cm	1.1 ± 0.2	1.1 ± 0.2	1.2 ± 0.3	0.003
LV mass, g	154 ± 49	166 ± 55	184 ± 70	0.001
LV mass index, g/m2	84 ± 26	89 ± 32	94 ± 31	0.008
Posterior wall thickness, cm	0.9 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	0.001
LV mean wall thickness, cm	1.0 ± 0.2	1.0 ± 0.2	1.1 ± 0.2	0.001
LV systolic function				
LVEF, %	62 ± 8	59 ± 9	57 ± 9.9	0.001
LV GLS, % (2ch)	-17.4 ± 3.1	-16.1 ± 3.2	-14.6 ± 3.3	0.001
E wave, cm/s	90 ± 27	91 ± 27	95 ± 29	0.19
A wave cm/s	78 ± 29	712 ± 26	71 ± 25	0.1
E/A ratio	1.3 ± 0.7	1.4 ± 0.8	1.4 ± 0.8	0.69
TDI septal a', cm/s	6.5 ± 1.9	6.3 ± 2.3	6.4 ± 2.4	0.81

TDI septal e', cm/s	5.6 ± 1.6	6.1 ± 2.0	5.8 ± 1.9	0.06
LA size and function				
LA diameter, cm	4.1 ± 0.6	4.2 ± 0.7	4.3 ± 0.7	0.06
LA area, cm2	22.6 ± 5.0	23.0 ± 6.8	23.1 ± 5.4	0.74
LA volume, ml	73 ± 27	74 ± 37	76 ± 30	0.57
LA volume index, ml/m2	40 ± 14	40 ± 29	40 ± 16	0.97
Pulmonary pressure and right ventricle				
TR velocity, m/s	2.7 ± 0.5	2.7 ± 0.5	2.7 ± 0.5	0.83
PASP, mmHg	35 ± 11	34 ± 11	35 ± 11	0.87
TAPSE, cm	2.0 ± 0.4	1.7 ± 0.4	1.7 ± 0.4	0.001
RVFAC, %	51 ± 9	48 ± 9	44 ± 9	0.001
RVEDA, cm2	20.2 ± 5.3	21.0 ± 5.8	21.6 ± 6.3	0.08
RVESA, cm2	9.9 ± 3.1	11.0 ± 3.9	12.3 ± 4.5	0.001

Baseline echocardiography by RVFWLS tertiles: Values are n, mean ± SD or median (interquartile range) unless otherwise specified.

A'= peak late velocity; e'= peak early diastolic mitral annular tissue velocity; E wave = peak early diastolic trans mitral flow velocity; LVESD = left ventricular end-systolic dimension; FAC = fractional area change; LA = Left atrial; LV=left ventricular, LVEDD= left ventricular end-diastolic dimension; LVEDVi= left ventricular end-diastolic volume indexed to body surface area; LVESD = LV ventricular end-systolic dimension; LVESVi = left ventricular systolic volume indexed to body surface area; PASP = pulmonary artery systolic pressure; RVEDA = right ventricular end-diastolic area; RVESA = right ventricular end-systolic area; RWT = relative wall thickness; s' = peak systolic mitral annular tissue velocity;

TAPSE = tricuspid annular plane systolic excursion; TDI = Tissue Doppler Imaging;

TR = tricuspid regurgitation, other abbreviations as in table 1

RVFWLS correlates with NTproBNP and LVEF

Figure 1.4 shows modest significant correlation between RVFWLS and left ventricular ejection fraction (r=-0.20, p<0.0001) and log NTproBNP (r=+0.20, p<0.0001)

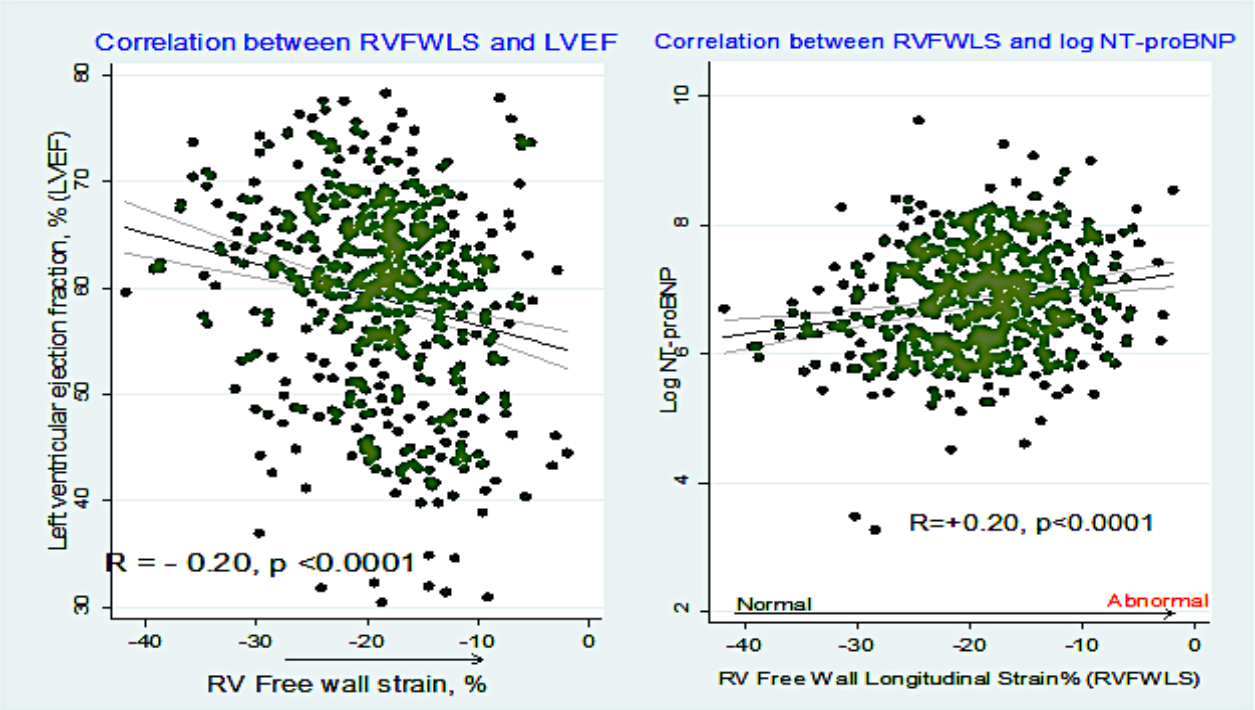

Figure 2.4: Two-way Scatter plot illustrating correlations between log NTproBNP, LVEF and RVFWLS; left ventricular ejection fraction (LVEF: left) and log transformed NTproBNP (right)

Table 2.3: Right ventricular free wall longitudinal strain and primary outcomes in PARAGON-HF

Outcome	Right Ventricular Free Wall Longitudinal Strain % (RVFWLS)			
Outcome	Continuous	Rvfwls<-21.4	-21.4<rvfwls<-15.9	Rvfwls>-15.9
Recurrent HFH/CV death,	277	78	90	109
Event rate (per 100 patient-years)	17.5 (14.4, 21.4)	13.9 (9.1, 21.7)	16.9 (12.4, 23.7)	22.8 (17.1, 31.1)
HR (unadjusted)	1.04 (1.01, 1.06), p=0.005	referent	1.44 (0.85, 2.45), p=0.17	1.96 (1.20, 3.19), p=0.007
aHR (adjusted[pp])	1.07 (1.02, 1.11), p=0.0001	referent	1.54 (0.79, 2.95), p=0.28	2.91 (1.56, 5.43), p=0.001
aHR (adjusted[1])	1.05 (1.02, 1.09), p=0.02	referent	1.24 (0.60, 2.54) p=0.56	2.19 (1.13, 4.2), p=0.020
Treatment effect (HR)		0.90 (0.43, 1.89) p=0.88	0.95 (0.48, 1.88), p=0.88	0.87 (0.50,1.51), p=0.61
First HHF	122	32	40	50
Event rate (per 100 patient-years)	8.7 (7.2, 10.3)	6.7 (4.7, 9.3)	8.3 (6.1, 11.4)	11.2 (8.5, 14.7)
HR (unadjusted)	1.04 (1.01, 1.06), p=0.014	referent	1.28 (0.81, 2.04) p=0.29	1.67 (1.10, 2.65), p=0.02
aHR (adjusted[pp])	1.05 (1.01, 1.09), p=0.023	referent	1.20(0.62, 2.30) p=0.59	1.95 (1.05, 3.61), p=0.03
aHR (adjusted[1])	1.03 (0.99, 1.08), p=0.14	referent	0.99 (0.41, 2.20), p=0.99	1.79 (0.86, 3.74), p=0.12
CV death (CVD)	47	8	22	17

Event rate (per 100 patient-years)	3.0 (2.2, 3.9)	1.5 (0.7, 3.0)	4.2 (2.7, 6.4)	3.1 (2.0, 5.1)
HR (unadjusted)	1.03 (0.99, 1.78), p=0.14	referent	2.77(1.24, 6.23), p=0.01	2.10 (0.91, 4.87), p=0.08
aHR (adjusted[pp])	1.06 (1.02, 1.10), p=0.004	referent	3.24(0.90, 11.6), p=0.07	2.68(0.71, 10.13), p=0.15
aHR (adjusted[1])	1.01 (0.93, 1.08), p=0.88	referent	4.18 (1.06, 16.5) p=0.04	2.19 (0.52, 9.14), p=0.28
1st HHF/CVD	139	37	48	54
Event rate (per 100 patient-years)	9.9 (8.4, 11.7)	7.6 (5.5, 0.5)	10.2 (7.7, 13.6)	11.9 (9.1, 15.6)
HR (unadjusted)	1.04 (1.01, 1.06), p=0.014	referent	1.33 (0.87, 2.05), p=0.19	1.56 (1.03, 2.37), p=0.04
aHR (adjusted[pp])	1.05 (1.01, 1.09), p=0.01	referent	1.42(0.76, 2.67), p=0.27	2.08 (1.13, 3.82), p=0.02
aHR (adjusted[1])	1.04 (0.98, 1.09), p=0.15	referent	1.25 (0.64, 2.44), p=0.51	1.67 (0.94, 3.59), p=0.08

HHF – Hospitalization for Heart failure, aHR – adjusted hazard ratio, HR – crude Hazard ratio
PP = adjusting for pulmonary artery systolic pressure or RV systolic afterload pressure
1 = adjusting for female gender, atrial fibrillation, diabetes, prior history of heart failure hospitalization, log NT-proBNP, left ventricular ejection fraction, pulmonary artery, heart rate and creatinine

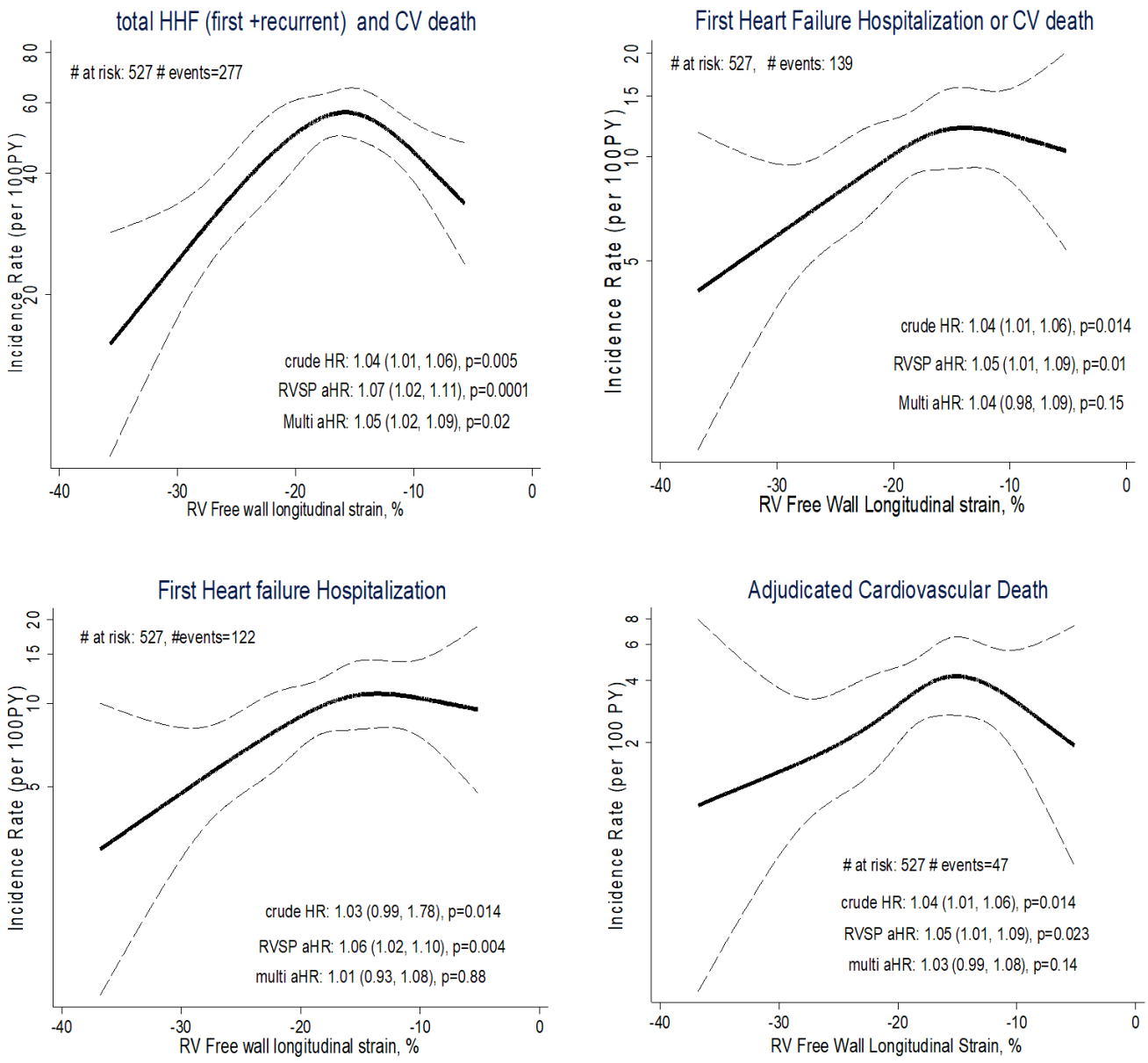

Figure 2.5: Restricted cubic spline with 4 knots showing linear trend of increasing events per 1% increase in RV free wall strain.

Multivariable adjusted incidence Rate (per 100 patient-years) by right ventricular free wall longitudinal strain for primary recurrent endpoint (upper left, p=0.02), first heart failure hospitalization or CV death (upper right, p=0.15), first heart failure hospitalization (lower left, p=0.09), and cardiovascular death (lower right)

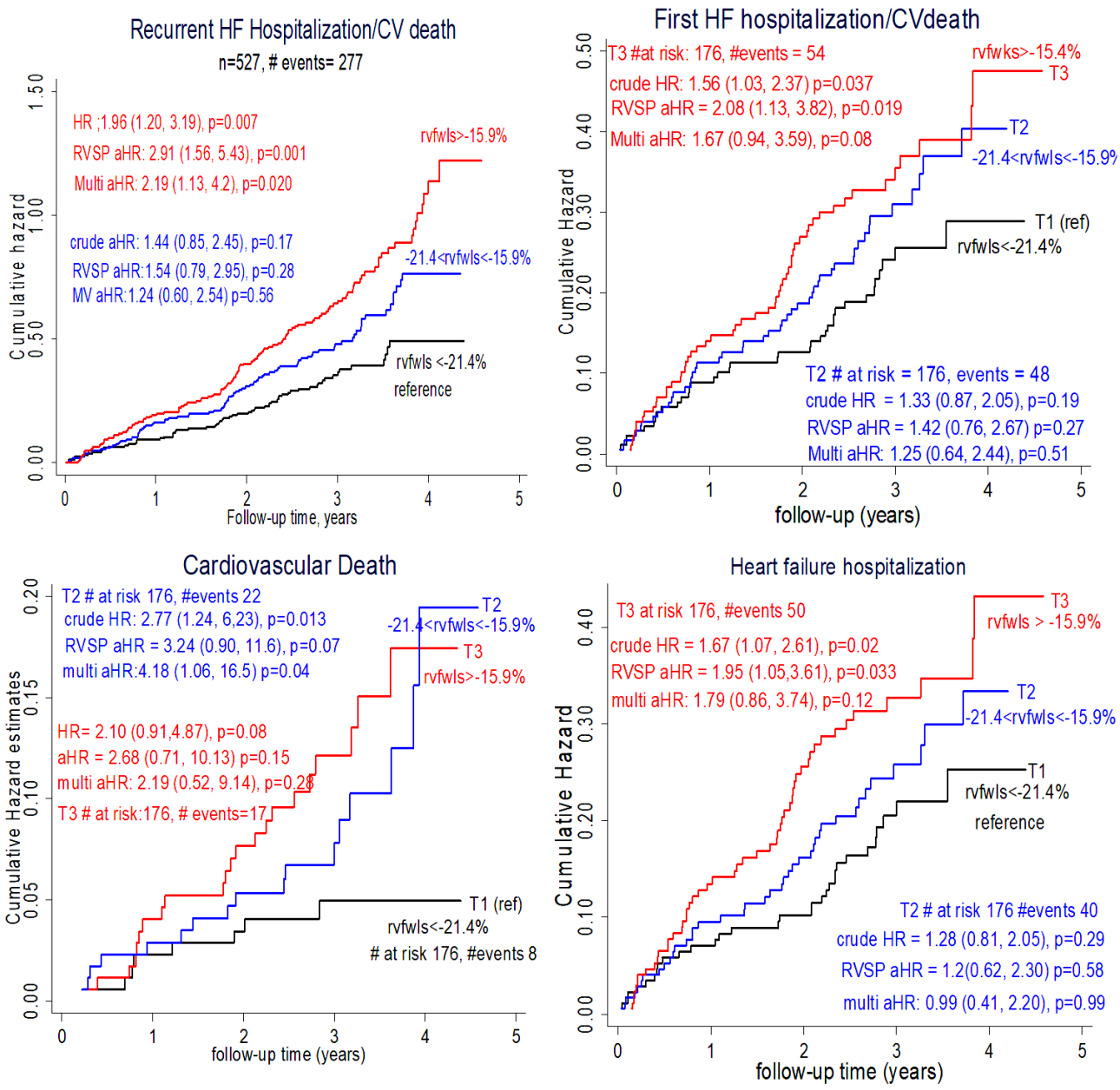

Figure 2.6: Cumulative Hazard for events across time of follow-up.

Using rvfwls < -21.4% as reference (black line), multivariable adjusted hazard ratios are reported for group in range -21.4<rvfwls>-15.6% (blue line) and rvfwls >-15.9% (red line). Outcomes are recurrent heart failure hospitalization or cardiovascular death (upper left), first heart failure hospitalization or cardiovascular death (upper right), First HF hospitalization,

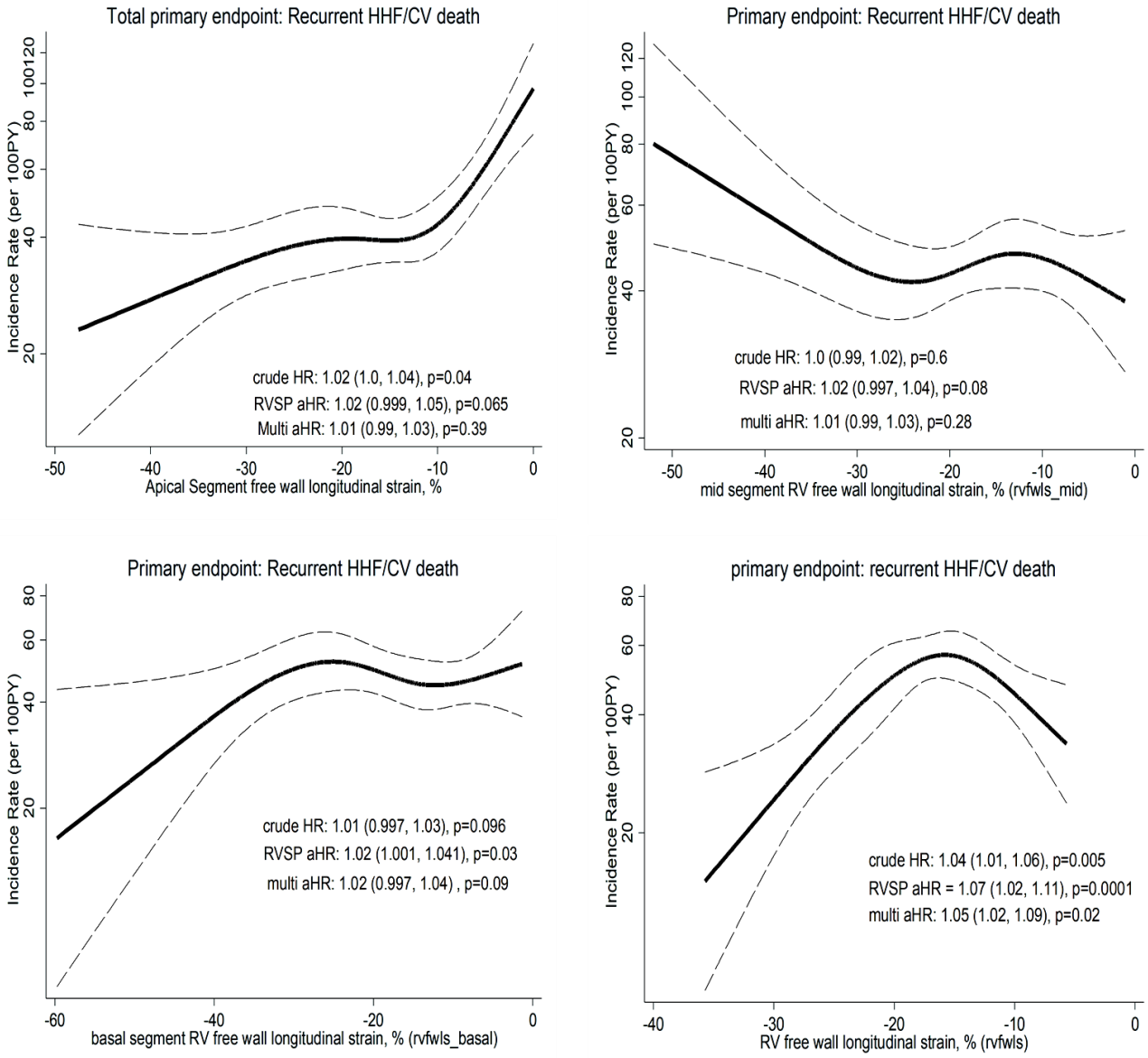

Figure 2.7: Restricted cubic spline with 4 knots showing linear trend of increasing event per 1% increase in segments of the lateral free wall region of the right ventricle

Multivariable adjusted incidence Rate (per 100 patient-years) by right ventricular free wall longitudinal strain for primary recurrent endpoint (upper left, p=0.02), first heart failure hospitalization or CV death (upper right, p=0.15), first heart failure hospitalization (lower left, p=0.09), and cardiovascular death (lower right)

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Supplementary Material:

Table 2.4: Supplementary Table 1: Comparing baseline characteristics by groups with RV strain, cardiac images without RV strain and no cardiac images no RV strain

	RV strain	Cardiac images no RV strain	No cardiac images	
	n=528	n=575	n=3698	
age, years (mean ± SD)	74.3 ± 7.9	73.0 ± 8.2	72.5 ± 8.5	0.001
female, N (%)	298 (56.5%)	290 (50.4%)	1891 (51.2%)	0.06
race, N (%)				0.001
ASIAN	82 (15.6%)	82 (14.3%)	443 (12.0%)	
BLACK OR AFRICAN AME	22 (4.2 %)	21 (3.7 %)	59 (1.6 %)	
OTHER	4 (0.8 %)	8 (1.4 %)	168 (4.5 %)	
WHITE	419 (79.5%)	464 (80.7%)	3024 (81.9%)	
region prim				0.001
Asia/Pacific and oath	95 (18.0%)	93 (16.2%)	574 (15.5%)	
Central Europe	99 (18.8%)	146 (25.4%)	1470 (39.8%)	
Latin America	2 (0.4 %)	15 (2.6 %)	353 (9.6 %)	
North America	192 (36.4%)	133 (23.1%)	234 (6.3 %)	
Western Europe	139 (26.4%)	188 (32.7%)	1063 (28.8%)	
Ischemic heart disease, N (%)	152 (28.8%)	175 (30.4%)	1396 (37.8%)	0.001
Atrial fibrillation, N (%)	181 (34.5%)	201 (35.1%)	1170 (31.8%)	0.16
Diabetes, N (%)	191 (36.2%)	244 (42.4%)	1627 (44.0%)	0.003
Hypertension, N (%)	491 (93.2%)	544 (94.6%)	3549 (96.1%)	0.005
Stroke, N (%)	59 (11.3%)	64 (11.1%)	385 (10.4%)	0.76

Prior HF hospitalization	259 (49.1%)	246 (42.8%)	1801 (48.8%)	0.025
History of MI	107 (20.3%)	126 (21.9%)	850 (23.0%)	0.35
NYHA, N (%)				0.49
2	383 (72.7%)	415 (72.2%)	2650 (71.7%)	
3	142 (26.9%)	159 (27.7%)	1016 (27.5%)	
4	2 (0.4 %)	1 (0.2 %)	28 (0.8 %)	
BMI	29.3 ± 4.9	30.3 ± 4.9	30.3 ± 5.0	0.001
Systolic BP, mmHg	128.3 ± 16.3	129.2 ± 15.6	131.1 ± 15.3	0.001
Heart rate, bpm, mean ± SD	69.0 ± 12.2	69.9 ± 12.4	70.7 ± 12.2	0.007
creatinine, mmol/L (mean ± SD)	101.3 ± 29.0	96.6 ± 26.9	95.7 ± 27.1	0.001
NTproBNP	1314.6 ± 1353.6	1210.5 ± 1090.4	1314.5 ± 1615.3	0.32
Ejection fraction from site	58.7 ± 7.5	58.3 ± 7.7	57.2 ± 7.9	0.001

NYHA = New York Heart Association, BP= Blood pressure, MI = Myocardial infarction, HF = Heart Failure

Supplementary table 2: Baseline echocardiographic characteristics by groups with rave strain, cardiac imaging no rave strain and no cardiac imaging

Table 2.5: Baseline echocardiographic characteristics by groups with RV strain, cardiac images and no strain,

	RV FWLS	Cardiac Images no RVFWLS	No Cardiac Images No RVFWLS	p value
	n=528	n=575	n=3698	
LVEDD, cm	4.5 ± 0.7	4.7 ± 0.6	5.0 ± 0.7	0.001
LVEDV, cm3	101.3 ± 37.8	103.3 ± 36.7	110.7 ± 44.6	0.26
LVESV, cm3	42.5 ± 22.4	44.5 ± 23.0	45.0 ± 21.9	0.4
LVEDD, cm	4.5 ± 0.7	4.7 ± 0.6	5.0 ± 0.7	0.001
LVESD, cm	3.3 ± 0.7	3.3 ± 0.7	3.1 ± 0.3	0.12
Septal wall thickness, cm	1.1 ± 0.2	1.1 ± 0.2	1.2 ± 0.3	0.41
LV mass, g	167.8 ± 59.8	171.0 ± 55.3	. ± .	0.36
LV mass index, g/m2	89.0 ± 30.0	89.8 ± 27.6	. ± .	0.66
Posterior wall thickness, cm	1.0 ± 0.2	0.9 ± 0.2	1.0 ± 0.2	0.09
LV mean wall thickness, cm	1.0 ± 0.2	1.0 ± 0.2	1.1 ± 0.1	0.51
LVEF, %	59.3 ± 9.3	58.3 ± 9.6	60.2 ± 8.3	0.21
seaperch	5.5 ± 1.4	5.6 ± 1.4	5.9 ± 1.2	0.1
mean_4ch_ls	388.6 ± 64.6	392.0 ± 63.7	388.8 ± 60.6	0.79
mean_2ch_ls	-16.1 ± 3.4	-16.1 ± 3.4	-16.2 ± 2.7	0.98

E wave, cm/s	92.0 ± 27.8	87.4 ± 28.0	86.5 ± 27.2	0.026
A wave cm/s	74.2 ± 27.3	72.9 ± 24.1	77.0 ± 30.2	0.56
E/A ratio	1.4 ± 0.8	1.3 ± 0.6	1.3 ± 0.8	0.15
TDI septal a', cm/s	6.4 ± 2.2	6.7 ± 2.0	7.2 ± 2.0	0.07
TDI septal e', cm/s	5.8 ± 1.8	5.7 ± 1.8	6.1 ± 2.1	0.47
EAratio	1.4 ± 0.8	1.3 ± 0.6	1.3 ± 0.8	0.15
LA diameter, cm	4.2 ± 0.7	4.3 ± 0.6	4.4 ± 0.7	0.07
LA area, cm2	22.9 ± 5.8	23.0 ± 5.1	23.5 ± 7.4	0.78
LA volume, ml	74.1 ± 31.6	75.6 ± 26.4	75.7 ± 33.0	0.72
LA volume index, ml/m2	39.9 ± 20.6	40.2 ± 14.8	37.0 ± 15.3	0.48
TR velocity, m/s	2.7 ± 0.5	2.6 ± 0.4	2.7 ± 0.5	0.29
PASP, mmHg	34.6 ± 11.1	33.2 ± 9.7	35.3 ± 10.4	0.28
TAPSE, cm	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4	0.75
RVFAC, %	47.4 ± 9.2	45.1 ± 9.6	46.5 ± 6.2	0.09
RVEDA, cm2	20.9 ± 5.8	21.6 ± 6.4	25.3 ± 11.0	0.12
RVESA, cm2	11.1 ± 4.0	11.9 ± 4.5	13.9 ± 7.3	0.045

Baseline echocardiography by RVFWLS tertiles: Values are n, mean ± SD or median (interquartile range) unless otherwise specified.

A'= peak late velocity; e'= peak early diastolic mitral annular tissue velocity; E wave = peak early diastolic trans mitral flow velocity; LVESD = left ventricular end-systolic dimension; FAC = fractional area change; LA = Left atrial; LV=left ventricular, LVEDD= left ventricular end-diastolic dimension; LVEDVi= left ventricular end-diastolic volume indexed to body surface area; LVESD = LV ventricular end-systolic dimension; LVESVi = left ventricular systolic volume

indexed to body surface area; PASP = pulmonary artery systolic pressure; RVEDA = right ventricular end-diastolic area; RVESA = right ventricular end-systolic area; RWT = relative wall thickness; s' = peak systolic mitral annular tissue velocity;

TAPSE = tricuspid annular plane systolic excursion; TDI = Tissue Doppler Imaging;

TR = tricuspid regurgitation, other abbreviations as in table 1

Table 2.6: Supplementary table 3: RVFWLS and other outcomes: cardiovascular hospitalizations and/or all cause-mortality

Outcome	RV deformation (continuous or tertiles)	Events	Event rate per 100 person-years	Unadjusted HR (CI)	P value	RV afterload adjusted HR (CI)	P value
All-cause death	Continuous	73	4.6 (3.7, 5.8)	1.03 (1.0, 1.07)	0.058	1.04 (0.98, 1.09)	0.17
	Normal (T1)	15	2.8 (1.7,4.7)	Reference	Reference	Ref	ref
	Mild (T2)	30	5.7 (4.0, 8.2)	2.02 (1.09, 3.76)	0.026	1.76 (0.75, 4.1)	0.20
	Moderate-Severe (T3)	28	5.3 (3.7, 7.7)	1.85 (0.99, 3.46)	0.056	1.75 (0.73, 4.2)	0.21
Total Primary composite = (1st HHF) + all cause death)	continuous	154	10.9 (9.3, 12.8)	1.03 (1.01, 1.06)	0.012	1.05 (1.01, 1.08)	0.012
	Normal (T1)	41	8.5 (6.2, 11.5)	-	-	-	-
	Mild (T2)	53	11.3 (8.6, 14.8)	1.33(0.88, 2.0)	0.17	1.34 (0.75, 2.4)	0.33

Moderate-Severe (T3)	60	13.2 (10.3, 17.0)	1.57(1.05, 2.33)	0.027	1.93 (1.03, 1.06)	0.023

Table 2.7: Reproducibility and reliability of RV myocardial strain of investigator with respect to reference measurements at the Cardiac imaging core lab

RVGLS	mean	Bias ± SD	Coefficient of Variation (CoV)	Interclass correlation
Interobserver				
Round 1	-15.81	-0.60± 3.08	-20%	0.84
Round 2	-15.55	-0.07± 1.57	-10%	0.96
Round 3	-15.37	0.28± 0.96	-6%	0.98
Intra observer	-15.40	0.33± 0.84	-5%	0.99

Summary

Heart failure with preserved ejection fraction (HFpEF) is quite common and associated with excess hospitalizations and mortality. Currently, there is no clinically effective therapy to reduce the excess mortality associated with HFpEF. Mechanisms underlying HFpEF have not been fully elucidated. A hallmark of HFpEF is heterogenous profiles and phenotypes in HFpEF patients, which may somewhat account for challenges in finding optimal treatment strategies. Regardless of phenotype, right ventricular dysfunction is common in HFpEF. Most of the studies conducted on RV in HFpEF are community-based, cross-sectional, have limited sample sizes and utilized conventional echocardiographic measurements. Experts dispute the consistency of these findings because; (1) load dependent conditions such as pulmonary hypertension are common in HFpEF and conventional methods may inaccurately estimate RVD due to known load and angle-limitations; (2) there is limited evidence from more robust RV measurements such as RV myocardial strain or 3D echocardiography; (3) To the best of our knowledge, among the limited HFpEF trials, there are no publications on RV myocardial strain.

I aimed to investigate RV myocardial strain in patients with HFpEF enrolled in the recently terminated PARAGON-HF trial. I screened a total of 1087 echocardiograms. 834 had at least one conventional RV systolic function measurement; tricuspid annular plane systolic excursion (TAPSE) or RV fractional area change (RVFAC). Of these, I conducted RV myocardial deformation analysis in 527 patients with HFpEF enrolled in PARAGON-HF. Myocardial strain parameters measured in this study were right ventricular global longitudinal strain (RVGLS) and right ventricular free wall longitudinal strain (RVFWLS).

In chapter 1, we aimed to (1) assess abnormalities in RV function estimated by both conventional echocardiographic and myocardial strain measurements, and the extent to which RV dysfunction was underestimated by conventional methods (2) Between measurements of RV myocardial

strain, how accurate could they predict abnormal conventional measurements and (3) association between RV myocardial strain and cardiovascular hospitalization and all-cause mortality. We found that RV abnormalities were frequent when estimated by RV myocardial strain compared to conventional echocardiographic methods. We also observed that even in the presence of normal conventional echocardiographic measurements, abnormal RV longitudinal strain was present in at least one half of corresponding participants. RVGLS was more sensitive but less specific to detect abnormal RVFAC and TAPSE. RVFLWS was less sensitive, more specific and was better calibrated to predict abnormal TAPSE and RVFAC. RVFWLS had better correlation to RV function estimates while RVFWLS was better correlated to LV function. We observed LV systolic function correlation to longitudinal strain peaked in septal wall segment. This may further explain the reason why RVGLS is less specific to detect abnormal TAPSE or RVFAC. Comparing group with normal to abnormal strain, groups defined by abnormal RVFWLS (>-19) showed significantly higher mortality, while this was less apparent in the groups defined by abnormal RVGLS (>-17%). As a continuous association, RVFWLS was associated with increased incidence and risk (hazard) of all-cause death. This trend was also less apparent for every percentage increase in RVGLS. Chapter 1 concluded with the findings that (1) conventional measurements underestimate RV dysfunction, by at least 50% (2) RVFWLS is a much more accurate, specific for RV function and less influenced by LV function (3) Incidence of outcomes were more apparent with RVFWLS. Overall, RVFWLS is a better surrogate of RV dysfunction and may have prognostic value. More studies are needed to validate and confirm these observations.

In Chapter 2, we aimed at investigating the relationship between RVFWLS and primary outcomes in PARAGON-HF trial. Specifically, we aimed at (1) assessing association of RVFWLS as a continuous function (2) Effect modification by stratifying the RVFWLS into tertiles (<-21.9%, -21.4 to 15.9%, >-15.9%). We found some differences in baseline characteristics and echocardiographic features at that patients in group with RVFWLS >-15.5=9% were more likely

to be male, have diabetes and atrial fibrillation. Patients with RVFWLS > 15.9% also had higher body mass index, heart rate, NTproBNP and creatinine but similar estimated meant glomerular filtration rate. There was a linear increase in incidence of first, recurrent heart failure hospitalizations and cardiovascular death with every % increase in RVFWLS even after accounting for pulmonary pressures and baseline differences. In segmental regional strain analysis, this trend was apparently similar in apical and basal segments. Patients with RVFLWS had at least two-times the risk of primary endpoint compared to patients with normal RVFWLS (<-21.4). Abnormalities in displacement of basal segment (TAPSE) have been reported to have prognostic value. This suggests that beyond basal free wall abnormalities, anomalies in the apical regional abnormalities may also be frequent in HEFpEF and contributive to poor outcomes. Overall, RVFWLS is independently associated with adverse outcomes in HFpEF, risk is about two-times higher if your RVFWLS falls in range of >-15.9%. This association may be driven by both anomalies in basal and apical segments of the RV.

Some limitations to be considered are (1) limited sample size in our study may have limited our power to test multivariable adjusted associations to individual adverse cardiovascular events (2) Missing data may have introduced sampling bias (3) Cardiac images from different site investigator may have introduced type 1 error. (4) hypothesis generating and limited generalizability of study findings from trial participants

Strengths were (1) PARAGON-HF largest recent trial with strict inclusion criteria and just recently terminated (2) to the best of our knowledge the first HFpEF trial to associate RVFWLS and adverse outcomes (3) Only one investigator trained to very high standards conducted all RV myocardial strain analyses. Intraclass correlation of 0.98 and <6% variation with imaging lab reference. (4) 527 participants with strain is a relatively large study considering that most RV studies rarely exceed 300 participants.

Overall, RV dysfunction is underestimated by conventional echocardiographic measurements. At least one of every two persons with HFpEF will have RV dysfunction even when conventional RV systolic measurements are normal. This suggests the additional diagnostic value of RV myocardial strain over conventional RV systolic measurements which are used routinely in clinical practice. This also reflects the presence of subclinical changes in RV. Similarly, longitudinal strain has been shown to be useful in diagnosing early left ventricular dysfunction. We further found that RVFWLS was a better predictor of the presence of abnormal conventional RV systolic measurements (RVFAC & TAPSE) and was least influenced by LV systolic function. These findings suggest RVFWLS is more reliable to detect RV abnormalities than RVGLS. These are consistent with expert consensus which clearly recommend RVFWLS in guidelines. Our observation in chapter 1 that adverse events were more apparent in RVFWLS than RVGLS, are further complimented by findings in chapter 2. We clearly find a trend of linear increase in adverse cardiovascular events (heart failure hospitalizations and cardiovascular death) for every increase in RVFWLS independent of pulmonary hypertension and baseline covariates. Thus, we considered RVFWLS a predictor of adverse outcomes in patients with HFpEF. Patients who exhibited impaired RVFWLS in range >-16 were more than two-times at risk of adverse cardiovascular events. Trend of increasing adverse events are similarly observed with basal segment and apical segment systolic strain. Further suggesting abnormalities in these regions seem to drive this association. Thus, may be potential targets for therapeutic innovation and intervention in HFpEF. In conclusion, RVFWLS may be clinically useful to (1) identify early or subclinical RV dysfunction (2) identify and stratify patients at risk of adverse cardiovascular events (3) segmental strain may be useful in identifying potential targets for therapeutic ventures whilst increasing our understanding of RV function in HFpEF and other diseases.

Future directions;

- Advanced imaging such as speckle tracking echocardiography provide more than just diagnostic utility but the scope to evaluate the right heart more detailly, thus, the potential to improve our understanding of cardiac remodeling. Further studies on the right ventricle are needed. Some of my on-going work and prospective tasks include but are not limited to the following
    - Exploring different RV myocardial strain patterns in different HFpEF phenotypes (Pulmonary hypertension, Diabetes, Obesity). Thus, potentially offering insight to underlying mechanisms.
    - Reporting on RV strain analyses already conducted in other studies at the CICL; MYOKARDIA HF (Already analyzed), PULSE PHT (Already analyzed), APPOLO (collaboration for RV strain imaging)
    - Other collaborations at and/or beyond the Cardiovascular Imaging Core Lab