


# Comparison of left ventricular longitudinal systolic function parameters in the prediction of adverse outcome in heart failure with preserved ejection fraction

Anna Goździk<sup>1</sup>, Thomas H. Marwick<sup>2,3</sup>, Monika Przewlocka-Kosmala<sup>1,2,3</sup>, Ewa A. Jankowska<sup>1</sup>, Piotr Ponikowski<sup>1</sup> and Wojciech Kosmala<sup>1,2,3\*</sup> 

<sup>1</sup>Wrocław Medical University, Borowska 213, Wrocław, 50-556, Poland; <sup>2</sup>Baker Heart and Diabetes Institute, Melbourne, Australia; <sup>3</sup>Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia

## Abstract

**Aims** Several different diagnostic parameters can be used to assess left ventricular (LV) longitudinal systolic function, but no studies comparing their predictive value have been conducted. We sought to compare the prognostic value of LV long-axis function parameters at rest and exercise using the population with heart failure with preserved ejection fraction (HFpEF).

**Methods and results** Clinical and biochemical variables were collected at baseline in 201 patients with HFpEF. Echocardiography was performed at rest and immediately after exercise, with measurement of mitral annular plane systolic excursion, systolic tissue velocity ( $s'$ ), global longitudinal strain (GLS), and global longitudinal strain rate (GLSR). Participants were followed for 48 (24–60) months for heart failure hospitalization and cardiovascular death. Seventy-four patients (36.8%) met the study endpoint. Cox regression analysis revealed that after adjustment for Meta-Analysis Global Group in Chronic Heart Failure risk score, brain natriuretic peptide (BNP), and peak  $VO_2$ , heart failure hospitalization and cardiovascular death were significantly associated with GLS at rest [hazard ratio (HR) 0.91; 95% confidence interval (CI) 0.84–0.98;  $P = 0.016$ ], GLS after exercise (HR 0.84; 95% CI 0.77–0.91;  $P < 0.001$ ), and GLSR after exercise (HR 0.13; 95% CI 0.04–0.48;  $P = 0.002$ ). The addition of each of the following: exercise GLS and GLSR and resting GLS to the base model including Meta-Analysis Global Group in Chronic Heart Failure, BNP, and peak  $VO_2$  improved predictive power for the study endpoint [net reclassification improvement (NRI) = 49%,  $P < 0.001$ ; NRI = 42%,  $P = 0.004$ ; and NRI = 38%,  $P = 0.009$ , respectively]. Exercise GLS was the only longitudinal parameter significantly improving  $c$ -statistics of the base model (0.68 vs. 0.73;  $P = 0.047$ ).

**Conclusions** Echocardiographic parameters of LV longitudinal function are not equipotential in predicting adverse outcomes in HFpEF. LV deformation indices, especially assessed with exercise, show the highest predictive utility independent from and incremental to clinical data and BNP.

**Keywords** Heart failure with preserved ejection fraction; LV longitudinal systolic function; Prognosis

Received: 5 November 2020; Revised: 10 January 2021; Accepted: 25 January 2021

\*Correspondence to: Prof. Wojciech Kosmala, Cardiology Department, Wrocław Medical University, Borowska 213, 50-556 Wrocław, Poland. Tel: +48 71 736 42 20; Fax: +48 71 736 42 09. Email: wojciech.kosmala@umed.wroc.pl

## Introduction

The longitudinal component of left ventricular (LV) mechanics represents an essential contributor to the overall cardiac performance. Abnormalities of longitudinal function appears early in the preclinical phase of myocardial impairment

and then progressively increases over the symptomatic stages of disease.<sup>1–5</sup> Derangements of LV longitudinal systolic function provide prognostic information that may be useful for defining patient management strategies in a variety of cardiovascular disorders, including heart failure (HF).<sup>6–13</sup> Myocardial deformation, tissue velocities, and mitral annular

displacement have provided different technical approaches to measuring LV longitudinal contraction. All have been effectively used for risk stratification,<sup>1,14–17</sup> but their comparative value remains unclear, as no studies comparing the predictive value of different longitudinal function measures have been reported to date.

Reductions in LV longitudinal function are predictive of adverse outcomes in HF with preserved ejection fraction (HFpEF<sup>18,19</sup>). The measurement of LV longitudinal systolic reserve at exercise may outperform resting assessment in prognostic evaluation of this clinical syndrome.<sup>20,21</sup> Accordingly, the aim of this study was to compare the prognostic utility of four echocardiographically derived LV longitudinal systolic function parameters: global longitudinal strain (GLS) and global longitudinal strain rate (GLSR), mitral annular systolic velocity ( $s'$ ), and mitral annular plane systolic excursion (MAPSE) measured at both rest and exercise using a well-characterized HFpEF population.

## Methods

### Patient selection

In this study, 201 patients satisfying the HFpEF criteria in place at the time of recruitment (i.e. between 2012 and 2015<sup>22</sup>) were recruited from hospital clinics at a tertiary cardiology centre (University Hospital, Wroclaw, Poland). Each participant underwent cardiopulmonary exercise testing, resting and immediate post-exercise echocardiography, and blood sampling for laboratory assessments.

The major inclusion criteria comprised (i) signs and symptoms of HF (dyspnoea, fatigue, and exercise intolerance) consistent with New York Heart Association Functional Class II or III, with reduced exercise capacity (<100% of age-predicted and sex-predicted normal ranges for peak oxygen consumption); (ii) preserved LV ejection fraction (>50%); and (iii) evidence of diastolic dysfunction according to the 2009 European Association of Echocardiography/American Society of Echocardiography criteria available at the time of recruitment [reduced  $e'$  (septal  $e' < 8$  cm/s and lateral  $e' < 10$  cm/s) and the presence of the following additional features: Grade I— $E/A < 1$ ,  $E/e' < 13$ , the time difference between atrial reversal wave of the pulmonary venous flow duration and mitral A-wave duration ( $\Delta A_{dur}$ ) <30 ms, and  $\Delta E/A$  during the Valsalva manoeuvre <0.5; Grade II— $E/A$  1–2 and at least two of the three abnormalities:  $E/e' \geq 13$ ,  $\Delta A_{dur} \geq 30$  ms, and  $\Delta E/A$  during the Valsalva manoeuvre  $\geq 0.5$ ; and Grade III— $E/A > 2.0$  and at least one of the two abnormalities:  $E/e' \geq 13$  and  $\Delta A_{dur} \geq 30$  ms].<sup>23</sup>

The exclusion criteria included (i) atrial fibrillation or flutter; (ii) ischaemic heart disease, defined by the presence of atherosclerotic lesions at coronary angiography or inducible

ischaemia during exercise testing (because myocardial ischaemia could limit exercise capacity without involving diastolic dysfunction); (iii) moderate and severe valvular heart disease; (iv) established or suspected pulmonary disease (vital capacity <80% or forced expiratory volume in 1 s being <80% of age-specific and sex-specific reference values); (v) haemoglobin <11 mg/dL; and (vi) other significant co-morbidities, including malignancy, renal failure, infections, and autoimmune, skeletal, and thyroid illnesses.

All study subjects were informed of the purpose of the study and provided written informed consent. The study was performed in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee.

### Outcome

Patients were followed over a median period of 48 (24–60) months for the composite endpoint of HF hospitalization (defined as hospital admission due to HF worsening requiring intensification of diuretic therapy) or cardiovascular death. This event rate was verified by regular contact with patients or their proxies.

The current analysis focused on the comparison of prognostic abilities of LV longitudinal systolic function parameters. A comprehensive evaluation of clinical risk in the studied HFpEF population covering a shorter follow-up was presented in our previous paper.<sup>20</sup>

### Echocardiography

Echocardiography imaging was performed using standard equipment (Vivid e9, General Electric Medical Systems, Milwaukee, WI, USA) with phased array 2.5 MHz multi-frequency transducer. Imaging data were analysed offline after being saved in the digital format on a secure server.

#### Conventional imaging

Cardiac dimensions and wall thicknesses were measured according to recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.<sup>24</sup> LV volumes and left atrial volumes were estimated by the biplane Simpson and area-length methods, respectively. LV end-diastolic and end-systolic volumes in the apical four-chamber and two-chamber views were used for calculation of ejection fraction.

#### Strain and strain rate

The assessment of LV longitudinal deformation was performed using a semi-automated two-dimensional speckle tracking technique (Echopac PC Version 113, General Electric Medical Systems, Horten, Norway) analysing all six segments of the left ventricle in the three apical views (four-chamber, two-chamber, and long-axis views) with temporal resolution

of 60–90 frames per second. After manually tracking the endocardial border and selecting appropriate wall thickness, the software automatically identified segments and tracked the motion of acoustic markers in each view. Segments with incorrect tracking were readjusted manually in the next step. LV deformation curves were automatically generated and displayed. The greatest negative values on the midmyocardial strain curve and on the strain rate curve during LV systole were measured, and averages from all analysable segments were displayed as GLS and GLSR, respectively.

The assessment of left atrial longitudinal deformation was carried out in the apical four-chamber and two-chamber views using the onset of QRS as the zero reference point. Left atrial reservoir strain was measured as the peak value during LV systole, and contractile strain was assessed as the value of strain at the onset of P wave in electrocardiogram. The final left atrial strain values were the averages from both apical views.

#### *Tissue systolic velocity*

Peak systolic tissue velocity ( $s'$ ) was assessed by pulsed-wave tissue Doppler at the septal and lateral aspects of the mitral annulus, and an average value from both sides was used in the analysis.

#### *Mitral annular plane systolic excursion*

Measurements were performed by M-mode from the apical four-chamber view at the septal and lateral border of the mitral annular plane, with the M-mode cursor line being positioned parallel to longitudinal LV motion. In case of the scan line misalignment, anatomical M-mode was used to correct the insonation angle. The total displacement was measured from the lowest point at end-diastole to aortic valve closure (end of the T wave on the electrocardiogram). The value of MAPSE averaged from both sides of the mitral annulus was used in the analysis.

The acquisitions for LV longitudinal function assessment were performed as a first part of post-test imaging and accomplished within 60–90 s after exercise termination.

#### *Assessment of left ventricular diastolic function*

Left ventricular inflow parameters including peak early (E) and late diastolic flow velocity (A) and deceleration time of early diastolic flow wave (DT) were evaluated from the apical four-chamber view by pulsed-wave Doppler with the sample volume placed between the tips of the mitral leaflets. Analogous to  $s'$ , peak early diastolic tissue velocity ( $e'$ ) was measured using pulsed-wave tissue Doppler at the septal and lateral segments of the mitral annulus. The ratio of mitral early diastolic velocity to the average  $e'$  velocity obtained from the septal and lateral portions of the mitral annulus ( $E/e'$ ) was calculated to approximate LV filling pressure.

All echocardiographic parameters were averaged over three consecutive cardiac cycles.

## Cardiopulmonary exercise testing and blood assays

Each participant underwent symptom-limited treadmill exercise testing using a modified Bruce protocol with standard electrocardiogram and blood pressure monitoring. Ventilation, oxygen uptake, and carbon dioxide production were monitored continuously, and peak oxygen uptake (peak  $VO_2$ ) was calculated as the average oxygen consumption during the last 30 s of exercise. Exercise capacity was also assessed in metabolic equivalents on the basis of the peak exercise intensity. Previous pharmacotherapy was maintained unchanged.

Peripheral venous blood samples were obtained for laboratory measurements including brain natriuretic peptide (BNP).

The Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score (including the following variables: age, gender, ejection fraction, creatinine, diabetes mellitus, chronic obstructive pulmonary disease, systolic blood pressure, body mass index, New York Heart Association class, angiotensin-converting enzyme inhibitor use, beta-blocker use, HF duration, and current smoker) was calculated for each participant to assess prognosis on the basis of clinical parameters.<sup>25</sup>

## Statistical analysis

Data are presented as mean  $\pm$  standard deviation for normally distributed variables, as median (inter-quartile range) for skewed variables (BNP), and as counts and percentages for categorical variables. Between-group comparisons of clinical and echocardiographic features in patients with and without events were made using univariable Cox regression. The associations of LV longitudinal systolic function parameters with the study endpoint were assessed with Cox proportional hazard models adjusted for MAGGIC risk score, BNP, and peak  $VO_2$ . A cause-specific competing risk approach was used for the outcome of interest (HF hospitalization or cardiovascular death) and the competing risk of non-cardiovascular death. Relative risks were expressed as hazard ratios with 95% confidence intervals (CIs). The incremental value of LV longitudinal systolic function parameters for the prediction of outcome was examined in nested Cox models by the addition of the parameter of interest (i.e. GLS, GLSR,  $s'$ , or MAPSE, each evaluated at rest and exercise) to a base model including the MAGGIC risk score, BNP, and peak  $VO_2$ . The change in overall log-likelihood ratio  $\chi^2$  was used to assess the increase in predictive power after the addition of LV longitudinal systolic function parameter. The generalized  $R^2$  was used to assess the explanatory power of each model. The relative quality of models was estimated by the Akaike information criterion. The  $c$ -statistic was used to evaluate model

performance. The significance of change in *c*-statistic after the addition of LV longitudinal systolic function parameter to the base model was evaluated using the bootstrap method with 2000 iterations for each test. The net reclassification improvement, calculated on the basis of category-free approach, was used to evaluate the magnitude of reclassification achieved after the addition of LV longitudinal systolic function parameter to a base model. The reproducibility of GLS, GLSR, *s'*, and MAPSE measurements was assessed by the Bland–Altman method (mean difference and 95% CI) and intraclass correlation coefficient. To facilitate the interpretation of the reproducibility of parameters acquired by different techniques, the Bland–Altman metrics were indexed to the mean value of test and retest measurements. Accordingly, the difference between test and retest was calculated as a percentage of the mean value of these measurements and, analogous to the non-index values, presented as mean difference and 95% CI. All analyses were carried out with standard statistical software (Statistica Version 13, TIBCO Software Inc., Palo Alto, CA, USA, and R software Version 3.5.3 (<http://cran.r-project.org/>)). Statistical significance was set at  $P < 0.05$ .

## Results

### Patient characteristics and events

During a median follow-up of 48 months, the study endpoint of hospitalization due to HF worsening or cardiovascular death occurred in 74 patients (36.8%). The overall mortality rate was 10.9% (22 patients). The cause of death was cardiac in 13 cases, cerebral stroke in three cases, and haematological malignancy, pneumonia, and septic shock—each in one case, and in three cases, the reason was not established. The demographic, clinical, and echocardiographic characteristics of patients with and without the endpoint are presented in *Table 1*. Primary, infiltrative, or storage disease-associated cardiomyopathy was not diagnosed in any study participant. The subset with events was characterized by older age, higher prevalence of diabetes, lower estimated glomerular filtration rate and exercise capacity, higher BNP and MAGGIC risk score, and more impaired left atrial function (lower reservoir and contractile strain), LV diastolic function (higher *E/e'* ratio at rest and exercise and larger left atrial size), and longitudinal systolic function (lower GLS, GLSR, *s'*, and MAPSE at both rest and exercise). Examples of LV longitudinal function parameters in patients with and without the study endpoint are presented in *Figure 1*.

Significant correlations with peak  $\text{VO}_2$  were found for exercise GLSR and exercise *s'*, but not for exercise MAPSE and exercise GLS (*Table 2*). The ability to discriminate peak  $\text{VO}_2 < 20$  mL/min/kg was highest for exercise GLSR (*Table 2*).

### Associations of left ventricular longitudinal systolic function parameters with outcome

In a series of univariate Cox proportional hazard models, all the four LV longitudinal systolic function metrics, that is, GLS, GLSR, *s'*, and MAPSE, assessed at both rest and exercise, were significantly associated with the study endpoint (*Figure 2*). A significant association with the investigated outcome was also demonstrated for GLS at rest ( $<16\%$  (hazard ratio 1.81; 95% CI 1.11–2.96;  $P = 0.018$ ). A series of Cox proportional hazards models adjusted for MAGGIC risk score, BNP, and peak  $\text{VO}_2$  revealed that the only resting LV longitudinal systolic function parameter significantly associated with the study endpoint was GLS. In the analogous models developed for LV longitudinal systolic function indices evaluated after exercise, two parameters—GLS and GLSR—proved to be significant predictors of HF hospitalization and cardiovascular death (*Table 3* and *Figure 3*).

### Incremental prognostic value of left ventricular longitudinal systolic function parameters

In the sequential Cox analysis, the addition of GLS and GLSR measured after exercise, as well as the addition of resting GLS to the model including MAGGIC risk score, BNP, and peak  $\text{VO}_2$ , resulted in a significant increase in the  $\chi^2$  values. On the other hand, a significant increase in *c*-statistics was noted only for exercise GLS. No significant incremental benefit was shown from adding GLSR assessed at rest, as well as MAPSE and *s'* evaluated at both rest and exercise to the previously mentioned base model (*Figure 3*).

### Reclassification improvement

The net reclassification improvement varied between 25% and 49% after addition of LV longitudinal systolic function parameters to the model including MAGGIC risk score, BNP, and peak  $\text{VO}_2$ . Statistical significance in these analyses was demonstrated only for GLS measured at both rest and exercise and GLSR measured at exercise (*Table 4*).

### Feasibility and reproducibility of echocardiography

During post-processing of the acquired data, 6% of all LV segments at rest and 11% after exercise were unsuitable for further analysis of myocardial deformation due to artefacts and signal noise. The degree of concordance of measurements of LV longitudinal systolic function parameters assessed in 15 randomly selected examinations is presented in *Table 5*.

**Table 1** Baseline demographic, clinical, and echocardiographic characteristics of the studied population stratified by the occurrence of heart failure hospitalization or cardiovascular death

	Without endpoint (n = 127)	With endpoint (n = 74)	P
Age (years)	62.7 ± 8.0	66.8 ± 8.3	0.001
Male sex, n (%)	33 (26%)	20 (27%)	0.74
Diabetes, n (%)	32 (25%)	33 (45%)	0.005
Hypertension, n (%)	118 (93%)	69 (93%)	0.74
BMI (kg/m <sup>2</sup> )	29.4 ± 4.2	30.0 ± 4.0	0.39
NYHA Class II, n (%)	103 (81%)	53 (72%)	0.08
NYHA Class III, n (%)	24 (19%)	21 (28%)	
Haemoglobin (g/dL)	13.8 ± 1.1	13.4 ± 1.0	0.06
eGFR (mL/min/1.73 m <sup>2</sup> )	68.4 ± 15.9	61.7 ± 14.5	0.008
BNP (pg/mL)	40 (23–74)	59 (34–155)	<0.001
Peak VO <sub>2</sub> (mL/min/kg)	16.0 ± 4.6	14.3 ± 4.7	0.03
VE/VCO <sub>2</sub> slope	27.5 ± 5.3	29.0 ± 6.5	0.06
AT VO <sub>2</sub> (mL/min/kg)	15.9 ± 6.8	14.3 ± 4.7	0.11
METs per protocol	5.9 ± 2.9	4.5 ± 2.6	0.004
MAGGIC risk score	13.8 ± 4.9	16.7 ± 4.9	<0.001
SBP exe (mmHg)	166 ± 22	166 ± 21	0.90
DBP exe (mmHg)	67 ± 13	66 ± 11	0.47
Beta-blockers, n (%)	88 (69%)	57 (77%)	0.30
Ca blockers, n (%)	46 (36%)	30 (40%)	0.57
ACEI/ARB, n (%)	119 (94%)	70 (95%)	0.79
Thiazides, n (%)	60 (47%)	40 (54%)	0.30
Loop diuretics, n (%)	20 (16%)	16 (22%)	0.23
LVMI (g/m <sup>2.7</sup> )	53.3 ± 13.3	56.8 ± 13.5	0.07
LAVI (mL/m <sup>2</sup> )	32.4 ± 9.5	36.0 ± 9.6	0.02
LA reservoir strain (%)	28.6 ± 6.8	25.9 ± 6.0	0.007
LA contractile strain (%)	14.2 ± 4.1	12.9 ± 4.0	0.04
RV free wall strain (%)	27.9 ± 7.1	26.6 ± 8.1	0.31
EF (%)	72.4 ± 7.7	72.5 ± 9.9	0.85
E/e' rest	10.8 ± 3.0	12.4 ± 4.2	<0.001
E/e' exe	14.4 ± 4.3	16.4 ± 5.5	0.005
GLS rest (%)	18.9 ± 2.9	17.6 ± 3.5	0.005
GLS exe (%)	20.9 ± 3.0	18.6 ± 3.4	<0.001
GLSR rest (%)	0.93 ± 0.20	0.86 ± 0.18	0.02
GLSR exe (%)	1.12 ± 0.22	0.98 ± 0.22	<0.001
s' rest (cm/s)	7.4 ± 1.3	6.9 ± 1.2	0.003
s' exe (cm/s)	9.9 ± 1.8	9.0 ± 1.7	<0.001
MAPSE rest (mm)	12.6 ± 1.8	11.7 ± 1.9	0.002
MAPSE exe (mm)	14.3 ± 2.1	13.3 ± 2.1	0.003

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AT, anaerobic threshold; BMI, body mass index; BNP, brain natriuretic peptide; DBP, diastolic blood pressure; E, early mitral inflow; e', early diastolic mitral annular velocity; EF, ejection fraction; eGFR, estimated glomerular filtration rate; exe, after exercise; GLS, global longitudinal strain; GLSR, global peak systolic strain rate; LA, left atrial; LAVI, left atrial volume index; LVMI, left ventricular mass index; MAPSE, mitral annular plane systolic excursion; METs, metabolic equivalents; NYHA, New York Heart Association; rest, at rest; RV, right ventricular; s', peak systolic mitral annular velocity; SBP, systolic blood pressure; VE/VCO<sub>2</sub>, ventilation vs. carbon dioxide production slope; VO<sub>2</sub>, oxygen uptake. Values are mean ± SD, median (inter-quartile range), or n (%).

## Discussion

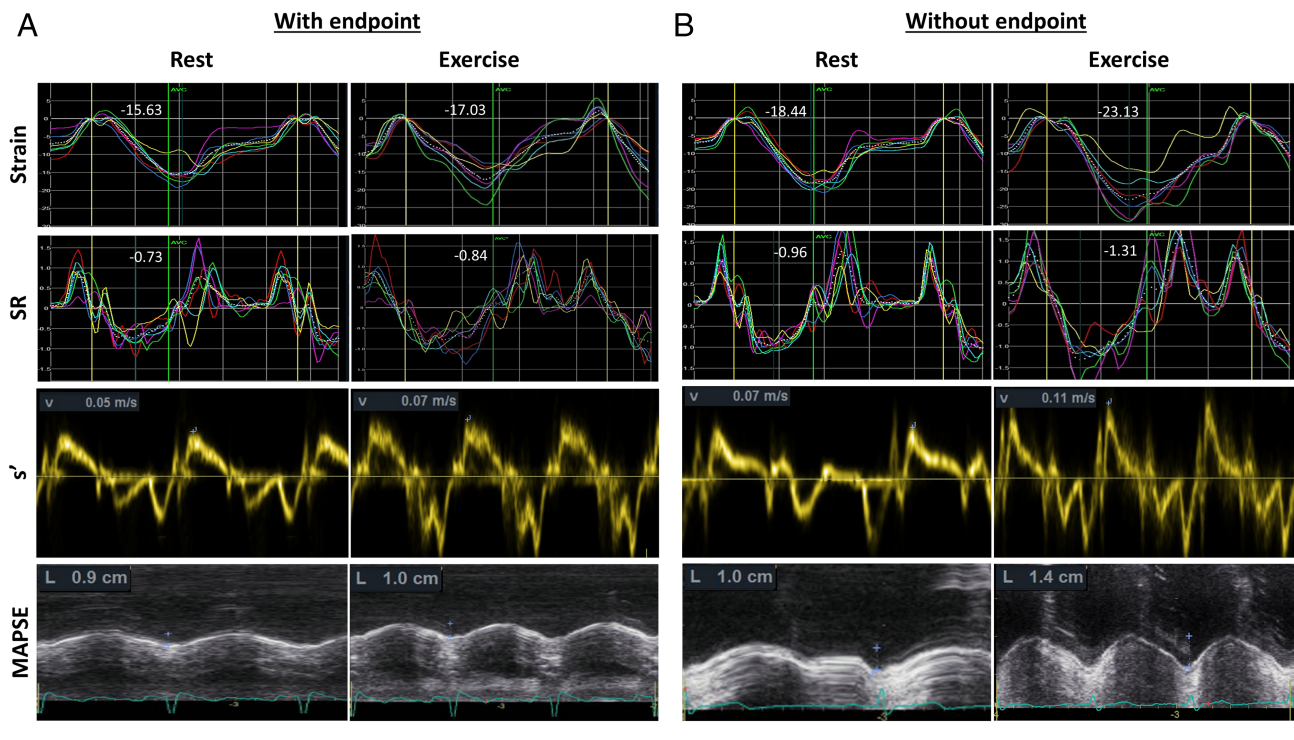
This study demonstrates that echocardiographic parameters of LV longitudinal systolic function are not equipotent in predicting adverse outcomes in HFpEF. LV deformation indices, especially assessed with exercise, show the highest predictive utility independent from and incremental to clinical data and BNP.

Left ventricular long-axis function contributes to both LV ejection and filling.<sup>14</sup> It is governed mainly by the subendocardial myocardial fibres, which are particularly vulnerable to injury due to the increased wall stress and disproportion between oxygen demand and supply, resulting in the

development of myocardial fibrosis.<sup>1</sup> Several parameters reflecting global LV longitudinal shortening, derived by different echocardiographic techniques, such as M-mode, tissue Doppler, and speckle tracking, have proven useful for diagnostic purposes. Indeed, GLS, systolic tissue velocity, and MAPSE all have prognostic significance in the general population and in a plethora of pathological conditions including HF, valvular and congenital heart disease, cardiomyopathies, diabetes, hypertension, and ischaemic heart disease.<sup>8–10,15,26–28</sup> Studies conducted in HF showed prognostic superiority of LV long-axis parameters over other echocardiographic measures of myocardial systolic function irrespective of the ejection fraction status.<sup>11–13,18,19</sup>



**Figure 1** Examples of left ventricular longitudinal function parameters in patients (A) with and (B) without the study endpoint. MAPSE, mitral annular plane systolic excursion;  $s'$ , peak systolic mitral annular velocity; SR, strain rate.



**Table 2** Association of different markers of LV function with peak  $VO_2$  and their discrimination of peak  $VO_2 < 20$  mL/min/kg

Parameter	Association with peak $VO_2$	AUC for prediction of peak $VO_2 < 20$ mL/min/kg	Optimal cutpoint	Sensitivity	Specificity
Exercise GLSR	$r = 0.27$ ; $P < 0.001$	0.68	$1.06 \text{ s}^{-1}$	61%	73%
Exercise $s'$	$r = 0.25$ ; $P < 0.001$	0.64	9.5 cm/s	55%	77%
Exercise MAPSE	$r = 0.14$ ; $P = 0.06$	0.61	14.0 mm	64%	60%
Exercise GLS	$r = 0.13$ ; $P = 0.08$	0.59	22.0%	84%	37%

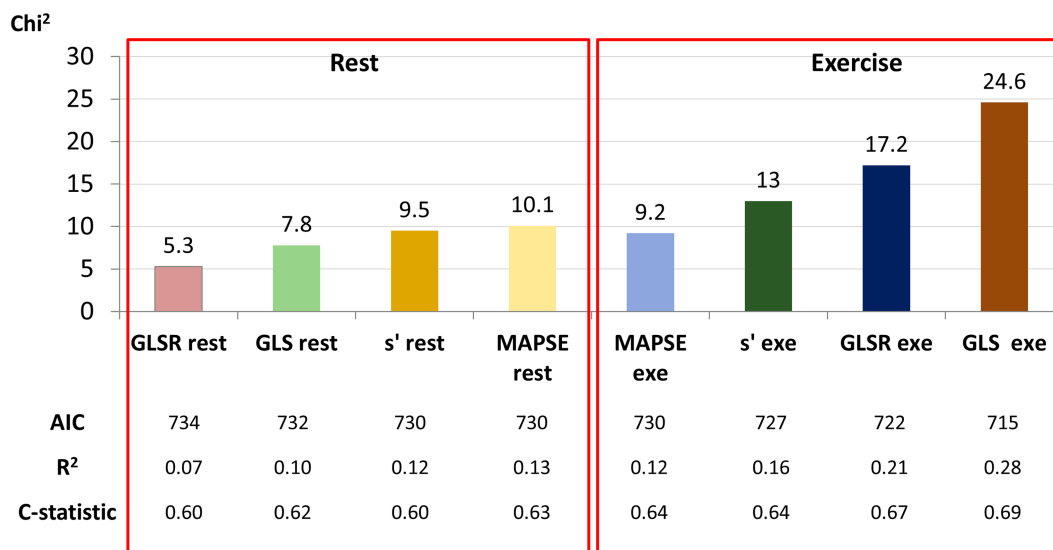
AUC, area under the curve; LV, left ventricular; other abbreviations as in Table 1.

Despite the abundance of single parameter-based studies, the selection of the most appropriate prognostication tool remains a matter of debate, with no evidence favouring one approach over the others. Our review of available literature shows the lack of direct comparisons of the predictive value of echocardiographic indices referring to LV long-axis systolic function. We demonstrated that when the evaluated parameters were measured in resting conditions, GLS was most effective as a prognosticator. In addition, assessment under an exercise load provided more prognostic information than at rest and also revealed superiority of LV deformation, especially GLS, which added a statistically significant incremental prognostic value to clinical data and BNP as confirmed by  $c$ -statistics. Furthermore, only GLS and GLSR measured at both rest and after exercise afforded a significant improvement in the accuracy of clinical risk classification based on MAGGIC risk score, BNP, and peak  $VO_2$ .

The superior prognostic value of LV deformation might be attributable to the fact that strain and strain rate are less susceptible to translational movement than  $s'$  and MAPSE and therefore might be more specific markers of myocardial systolic function. In addition, the assessment of LV longitudinal deformation across the entire LV myocardium may provide more adequate information than the assessment of systolic descent of the mitral annulus by  $s'$  and MAPSE. The prognostic relevance of LV longitudinal response to exercise in HFpEF underpins the notion that diminished LV systolic reserve might be more important than abnormalities of myocardial performance at rest. Accordingly, exertional measurements of LV longitudinal function might improve risk evaluation in this HF category.

It should be emphasized that the absolute differences in LV longitudinal function parameters between the subsets with and without the endpoint were small, which might be

**Figure 2** Predictive ability of left ventricular longitudinal systolic function parameters for heart failure hospitalization or cardiovascular death in the studied population. AIC, Akaike information criterion; GLS, global longitudinal strain; GLSR, global longitudinal strain rate; MAPSE, mitral annular plane systolic excursion; s', peak systolic mitral annular velocity.



**Table 3** Associations of left ventricular longitudinal systolic function parameters with the study endpoint in Cox proportional hazard models

Parameter	Unadjusted		Adjusted for MAGGIC risk score, BNP, and peak VO <sub>2</sub>	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
GLS rest	0.90 (0.83–0.97)	0.005	0.91 (0.84–0.98)	0.016
GLSR rest	0.24 (0.07–0.83)	0.02	0.29 (0.08–1.03)	0.056
s' rest	0.74 (0.61–0.90)	0.003	0.84 (0.69–1.03)	0.106
MAPSE rest	0.82 (0.73–0.92)	0.002	0.90 (0.79–1.02)	0.106
GLS exe	0.82 (0.76–0.89)	<0.001	0.84 (0.77–0.91)	<0.001
GLSR exe	0.09 (0.03–0.30)	<0.001	0.13 (0.04–0.48)	0.002
s' exe	0.90 (0.83–0.97)	<0.001	0.86 (0.74–1.01)	0.064
MAPSE exe	0.24 (0.07–0.83)	0.003	0.92 (0.81–1.03)	0.144

CI, confidence interval; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; other abbreviations as in Table 1. The data for each variable in Table 2 come from a separate model including MAGGIC risk score, BNP, peak VO<sub>2</sub>, and left ventricular longitudinal systolic function parameter.

attributable to a moderately severe progression of cardiovascular pathologies at baseline. However, this might affect the ability of these indices to be effectively implemented in clinical practice, including determining usable cut-off values for worse prognosis, and warrants further investigation.

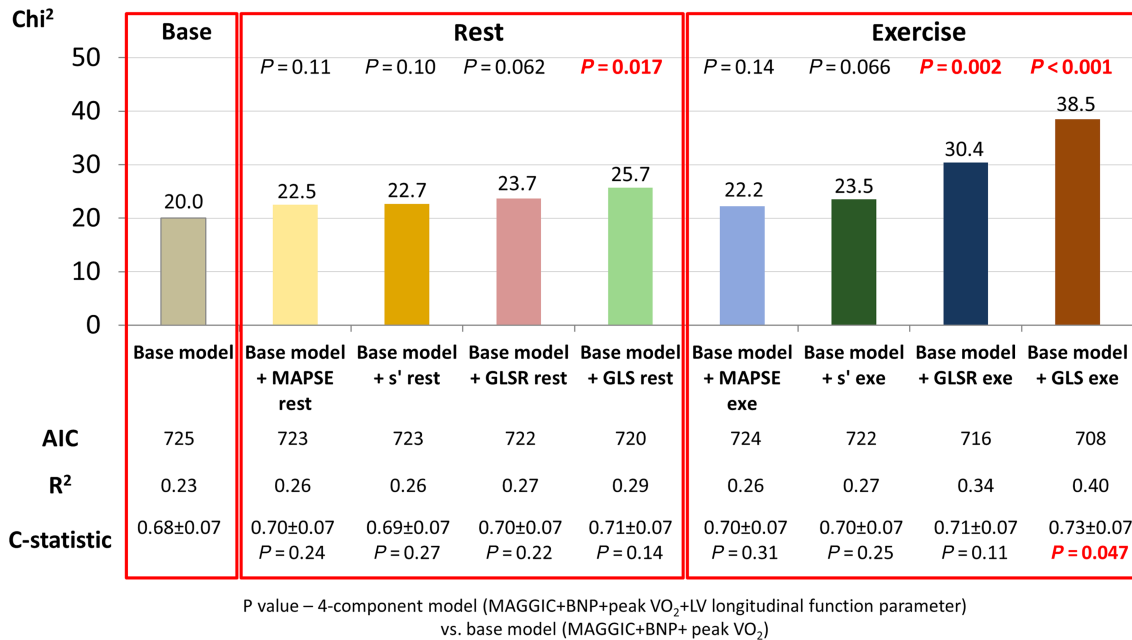
Among an increasing number of studies using cardiovascular magnetic resonance, little comparative data exist with respect to the prognostic assessment of LV long-axis function parameters.<sup>29–31</sup> A very recent paper revealed that both lateral MAPSE and feature tracking GLS independently contributed to risk prediction in hypertensive patients, which implies that these indices may supply complementary prognostic information.<sup>32</sup> We did not show any analogous

relationship in our analysis, which might be explained by between-modality and patient clinical profile differences.

### Limitations

First, the exclusion of patients with atrial fibrillation and myocardial ischaemia might limit generalization of our results to all subjects with HFpEF. Second, the recognition of HFpEF was based solely on the clinical data, with no verification by invasive measurements, which might limit in some cases a definite ascertainment of diagnosis. Third, the relatively low temporal resolution of exercise imaging might

**Figure 3** Incremental value of left ventricular (LV) longitudinal systolic function parameters for prediction of heart failure hospitalization or cardiovascular death. AIC, Akaike information criterion; BNP, brain natriuretic peptide; GLS, global longitudinal strain; GLSR, global longitudinal strain rate; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure risk score; MAPSE, mitral annular plane systolic excursion; s', peak systolic mitral annular velocity.



**Table 4** NRI after the addition of left ventricular longitudinal systolic function parameter to the basal model including MAGGIC risk score, BNP, and peak VO<sub>2</sub>

Parameter	NRI	P
<b>Rest</b>		
GLS	38%	0.009
GLSR	28%	0.060
s'	26%	0.078
MAPSE	25%	0.089
<b>Exercise</b>		
GLS	49%	<0.001
GLSR	42%	0.004
s'	27%	0.066
MAPSE	26%	0.070

MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; NRI, net reclassification improvement; other abbreviations as in Table 1.

have affected the accuracy of GLSR measurements. Fourth, a single-centre patient enrolment might constrain the external validity of our findings. Fifth, the extrapolation of our results to other cardiovascular pathologies is uncertain, especially in conditions more affecting annular velocities and displacement than myocardial deformation, like mitral valve disease or annular calcifications. Because of the inter-modality differences, the results of this paper cannot be directly extrapolated to studies using CMR techniques. Finally, GLS as defined in the recent consensus paper was based on peak strain throughout the LV region of interest, rather than the averaged regional strain used in our work. We planned the latter approach for two reasons—first, to enable us to remove segments where tracking was

**Table 5** Reproducibility of LV longitudinal systolic function parameters

		Bland–Altman		Indexed Bland–Altman		ICC	
		Intraobserver	Intraobserver	Interobserver	Interobserver	Intraobserver	Interobserver
GLS	Rest	0.1 (–0.4 to 0.5)	0.3 (0.3 to 1.0)	0.3 (–2.7 to 3.3)	1.7 (0.8 to 4.1)	0.94	0.91
	Exercise	0.2 (–0.2 to 0.6)	–0.2 (–0.9 to 0.5)	3.1 (–2.1 to 8.4)	–2.7 (–7.1 to 1.7)	0.97	0.97
GLSR	Rest	0.03 (–0.01 to 0.06)	0.05 (–0.01 to 0.09)	3.0 (–1.0 to 7.0)	5.6 (–0.6 to 10.7)	0.92	0.88
	Exercise	–0.01 (–0.06 to 0.08)	0.05 (–0.04 to 0.14)	–0.1 (–7.3 to 7.2)	3.7 (–3.8 to 11.2)	0.96	0.91
s'	Rest	0.14 (–0.09 to 0.37)	–0.39 (–0.81 to 0.03)	2.4 (–0.9 to 5.7)	–5.1 (–10.3 to 0.2)	0.97	0.94
	Exercise	–0.07 (0.41 to 0.27)	–0.32 (–0.88 to 0.24)	–0.1 (3.4 to 3.2)	–3.3 (–9.4 to 2.8)	0.98	0.92
MAPSE	Rest	0.20 (–0.49 to 0.90)	0.16 (–0.40 to 0.72)	2.3 (–3.9 to 8.4)	0.8 (–4.7 to 6.2)	0.90	0.91
	Exercise	0.28 (–0.24 to 0.81)	–0.62 (–1.25 to 0.01)	1.8 (–2.1 to 5.6)	–4.9 (–9.7 to 0.1)	0.94	0.89

ICC, intraclass correlation coefficient; LV, left ventricular; other abbreviations as in Table 1.

Indexed Bland–Altman—mean difference and 95% confidence interval after indexation to the mean value of test and retest measurements.



inadequate, and in order to make our measurement of regional contraction reflective of function, irrespective of conduction disturbances.

## Conclusions

The abilities of echocardiographic parameters of LV long-axis systolic function to stratify clinical risk in HFpEF are not equivalent. LV deformation seems to be the most reasonable prognostic marker of long-axis performance in this disease setting. Potential differences favouring the use of myocardial deformation indices are more apparent for measurements carried out under an exercise load. The improvement of predictive value of these parameters during the assessment at stress

may provide a rationale for the inclusion of exercise echocardiography to prognostic evaluation in HFpEF.

## Conflict of interest

None declared.

## Funding

This work was supported by Wroclaw Medical University, Wroclaw, Poland (ST-678), and the Royal Hobart Hospital Research Foundation, Hobart, Tasmania, Australia (13-024).

## References

- Henein MY, Gibson DG. Long axis function in disease. *Heart* 1999; **81**: 229–231.
- de Knecht MC, Biering-Sorensen T, Sogaard P, Sivertsen J, Jensen JS, Mogelvang R. Concordance and reproducibility between M-mode, tissue Doppler imaging, and two-dimensional strain imaging in the assessment of mitral annular displacement and velocity in patients with various heart conditions. *Eur Heart J Cardiovasc Imaging* 2014; **15**: 62–69.
- Suzuki K, Akashi YJ, Mizukoshi K, Mizukoshi K, Kou S, Takai M, Izumo M, Hayashi A, Ohtaki E, Nobuoka S, Miyake F. Relationship between left ventricular ejection fraction and mitral annular displacement derived by speckle tracking echocardiography in patients with different heart diseases. *J Cardiol* 2012; **60**: 55–60.
- Mogelvang R, Sogaard P, Pedersen SA, Olsen NT, Schnohr P, Jensen JS. Tissue Doppler echocardiography in persons with hypertension, diabetes, or ischaemic heart disease: the Copenhagen City Heart Study. *Eur Heart J* 2009; **30**: 731–739.
- García EH, Perna ER, Farías EF, Obregón RO, Macin SM, Parras JL, Agüero MA, Moratorio DA, Pitzus AE, Tassano EA, Rodríguez L. Reduced systolic performance by tissue Doppler in patients with preserved and abnormal ejection fraction: new insights in chronic heart failure. *Int J Cardiol* 2006; **108**: 181–188.
- Kearney LG, Lu K, Ord M, Patel SK, Profitis K, Matalanis G, Burrell LM, Srivastava PM. Global longitudinal strain is a strong independent predictor of all-cause mortality in patient with aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2012; **13**: 827–833.
- Iacoviello M, Puzzone A, Guida P, Forleo C, Monitillo F, Catanzaro R, Lattarulo MS, Antoncetti V, Favale S. Independent role of left ventricular global longitudinal strain in predicting prognosis of chronic heart failure patients. *Echocardiography* 2013; **30**: 803–811.
- Ballo P, Barone D, Bocelli A, Motto A, Mondillo S. Left ventricular longitudinal systolic dysfunction is an independent marker of cardiovascular risk in patients with hypertension. *Am J Hypertens* 2008; **21**: 1047–1054.
- Narayanan A, Aurigemma GP, Chinali M, Hill JC, Meyer TE, Tighe DA. Cardiac mechanics in mild hypertensive heart disease: a speckle-strain imaging study. *Circ Cardiovasc Imaging* 2009; **2**: 382–390.
- Saito M, Khan F, Stoklosa T, Iannaccone A, Negishi K, Marwick TH. Prognostic implications of LV strain risk score in asymptomatic patients with hypertensive heart disease. *JACC Cardiovasc Imaging* 2016; **9**: 911–921.
- Nikitin NP, Loh PH, Rd S, Ghosh J, Khaleva OY, Goode K, Rigby AS, Alamgir F, Clark AL, Cleland JGF. Prognostic value of systolic mitral annular velocity measured with Doppler tissue imaging in patients with chronic heart failure caused by left ventricular systolic dysfunction. *Heart* 2006; **92**: 775–779.
- Sengeløv M, Jørgensen PG, Jensen JS, Bruun NE, Olsen FJ, Fritz-Hansen T, Nochioka K, Biering-Sørensen T. Global longitudinal strain is a superior predictor of all-cause mortality in heart failure with reduced ejection fraction. *JACC Cardiovasc Imaging* 2015; **8**: 1351–1359.
- Nahum J, Bensaid A, Dussault C, Macron L, Clémence D, Bouhemad B, Monin JL, Dubois Rande JL, Gueret P, Lim P. Impact of longitudinal myocardial deformation on the prognosis of chronic heart failure patients. *Circ Cardiovasc Imaging* 2010; **3**: 249–256.
- Carlsson M, Ugander M, Mosen H, Buhre T, Arheden H. Atrioventricular plane displacement is the major contributor to left ventricular pumping in healthy adults, athletes, and patients with dilated cardiomyopathy. *Am J Physiol Heart Circ Physiol* 2007; **292**: H1452–H1459.
- Hu K, Liu D, Herrmann S, Niemann M, Gaudron PD, Voelker W, Ertl G, Bijnens B, Weidemann F. Clinical implication of mitral annular plane systolic excursion for patients with cardiovascular disease. *Eur Heart J Cardiovasc Imaging* 2013; **14**: 205–212.
- Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. *Heart* 2014; **100**: 1673–1680.
- Mogelvang R, Sogaard P, Pedersen SA, Olsen NT, Marott JL, Schnohr P, Goetze JP, Jensen JS. Cardiac dysfunction assessed by echocardiographic tissue Doppler imaging is an independent predictor of mortality in the general population. *Circulation* 2009; **119**: 2679–2685.
- Shah AM, Claggett B, Sweitzer NK, Shah SJ, Anand IS, Liu L, Pitt B, Pfeffer MA, Solomon SD. Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone. *Circulation* 2015; **132**: 402–414.

19. Shin HW, Kim H, Son J, Yoon HJ, Park HS, Cho YK, Han CD, Nam CW, Hur SH, Kim YN, Kim KW. Tissue Doppler imaging as a prognostic marker for cardiovascular events in heart failure with preserved ejection fraction and atrial fibrillation. *J Am Soc Echocardiogr* 2010; **23**: 755–761.
20. Kosmala W, Przewlocka-Kosmala M, Rojek A, Mysiak A, Dabrowski A, Marwick TH. Association of abnormal left ventricular functional reserve with outcome in heart failure with preserved ejection fraction. *JACC Cardiovasc Imaging* 2018; **11**: 1737–1746.
21. Wang J, Fang F, Wai-Kwok Yip G, Sanderson JE, Feng W, Xie JM, Luo XX, Lee APW, Lam YY. Left ventricular long-axis performance during exercise is an important prognosticator in patients with heart failure and preserved ejection fraction. *Int J Cardiol* 2015; **178**: 131–135.
22. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007; **28**: 2539–2550.
23. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur Heart J Cardiovasc Imaging* 2009; **10**: 165–193.
24. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 233–270.
25. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Køber L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J* 2013; **34**: 1404–1413.
26. Rydberg E, Arlbrandt M, Gudmundsson P, Erhardt L, Willenheimer R. Left atrio-ventricular plane displacement predicts cardiac mortality in patients with chronic atrial fibrillation. *Int J Cardiol* 2003; **91**: 1–7.
27. Brand B, Rydberg E, Ericsson G, Gudmundsson P, Willenheimer R. Prognostication and risk stratification by assessment of left atrioventricular plane displacement in patients with myocardial infarction. *Int J Cardiol* 2002; **83**: 35–41.
28. Svealy BG, Olofsson EL, Andersson B. Ventricular long-axis function is of major importance for long-term survival in patients with heart failure. *Heart* 2008; **94**: 284–289.
29. Romano S, Judd RM, Kim RJ, Kim HW, Klem I, Heitner JF, Shah DJ, Jue J, White BE, Indorkar R, Shenoy C, Farzaneh-Far A. Feature-tracking global longitudinal strain predicts death in a multicenter population of patients with ischemic and nonischemic dilated cardiomyopathy incremental to ejection fraction and late gadolinium enhancement. *JACC Cardiovasc Imaging* 2018; **11**: 1419–1429.
30. Romano S, Judd RM, Kim RJ, Kim HW, Klem I, Heitner JF, Shah DJ, Jue J, Farzaneh-Far A. Left ventricular long-axis function assessed with cardiac cine MR imaging is an independent predictor of all-cause mortality in patients with reduced ejection fraction: a multicenter study. *Radiology* 2018; **286**: 452–460.
31. Rangarajan V, Chacko SJ, Romano S, Jue J, Jariwala N, Chung J, Farzaneh-Far A. Left ventricular long axis function assessed during cine-cardiovascular magnetic resonance is an independent predictor of adverse cardiac events. *J Cardiovasc Magn Reson* 2016; **18**: 35.
32. Romano S, Judd RM, Kim RJ, Kim HW, Heitner JF, Shah DJ, Devereux RB, Salazar P, Trybula M, Chia RC, Evans K, Farzaneh-Far A. Prognostic implications of mitral annular plane systolic excursion in patients with hypertension and a clinical indication for cardiac magnetic resonance imaging: a multicenter study. *JACC Cardiovasc Imaging* 2019; **12**: 1769–1779.