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the Copenhagen City Heart Study

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Layer-Specific Global Longitudinal Strain and the Risk of Heart Failure and Cardiovascular Mortality in the General Population: The Copenhagen City Heart Study.

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Abstract

Aims: Layer-specific global longitudinal strain (GLS) has been demonstrated to predict outcome in various patient cohorts. However, little is known regarding the prognostic value of layer-specific GLS in the general population and whether different layers entail differential prognostic information. The aim of the present study was to investigate the prognostic value of whole wall (GLS_{ww}), endomyocardial (GLS_{Endo}), and epimyocardial (GLS_{Epi}) GLS in the general population.

Method: A total of 4,013 citizens were included in the present study. All 4,013 had 2D-speckle tracking echocardiography performed and analyzed. Outcome was a composite endpoint of incident heart failure (HF) and/or cardiovascular death (CVD).

Results: Mean age was 56 years and 57% were female. During a median follow-up time of 3.5 years, 133 participants (3.3%) reached the composite outcome. Sex modified the relationship between all GLS parameters and outcome. In sex stratified analysis, no GLS parameter remained significant predictors of outcome in females. In contrast, GLS_{ww} (HR=1.16, 95% CI [1.02;1.31], per 1% decrease) and GLS_{Epi} (HR=1.19, 95% CI [1.04;1.38], per 1% decrease) remained as significant predictors of outcome in males after multivariable adjustment (including demographic, clinical, biochemistry, and echocardiographic parameters). Lastly, only in males did GLS parameters provide incremental prognostic information to general population risk models.

Conclusions: In the general population, sex modifies the prognostic value of GLS resulting in GLS_{Epi} being the only layer-specific prognosticator in males, while no GLS parameter provides independent prognostic information in females.

Keywords: 2D-speckle tracking echocardiography; heart failure; cardiovascular death; layer-specific global longitudinal strain; general population

Introduction

During the last two decades, whole wall global longitudinal strain (GLS) has become a well-established prognostic marker of cardiovascular morbidity and mortality^{1,2}. The measure has repeatedly been demonstrated to be a superior predictor of long-term risk of cardiovascular outcome compared to the guidelines recommended measurement - left ventricular (LV) ejection fraction¹⁻⁴. Additionally, several studies have found GLS to be a stronger prognosticator in males than in females^{2,3}. Advances in two-dimensional speckle tracking echocardiography (2DSTE) software has made it possible for layer-specific GLS tracking. The prognostic value of layer-specific GLS has already been investigated in few studies^{1,5-7}. General consensus among the reported studies is that layer-specific GLS does provide significant prognostic information regarding cardiovascular outcome. Only one of these studies investigated layer-specific GLS in the general population. However, this study included a substantially smaller study sample and investigated a heterogeneous outcome, including coronary events, fatal and nonfatal heart failure (HF), pulmonary heart disease, new-onset atrial fibrillation, and life-threatening arrhythmias.

In this study, we hypothesize that there is valuable prognostic information to be gained by using layer-specific GLS to predict incident HF and cardiovascular death (CVD) in a low-risk general population. Discrimination of deformation between the different myocardial layers may facilitate detection of more subtle changes in myocardial contraction compared to whole wall GLS (GLS_{ww}). The potential incremental prognostic value could be explained by layer-specific affection of cardiac pathologies or a more representative quantification of myocardial status. Additionally, as previous studies have indicated that sex modifies the relationship between GLS_{ww} and cardiovascular morbidity and mortality^{2,3} we hypothesize that this is also the case for endomyocardial (GLS_{Endo}) and epimyocardial GLS (GLS_{Epi}). Further establishment of GLS parameters as a sex-dependent prognosticator, could contribute to better echocardiographic risk-stratification for both sexes.

Method

Population

The present study includes participants of the 5th Copenhagen City Heart Study. The Copenhagen City Heart Study is a prospective longitudinal cohort study on cardiovascular disease and risk factors in the general population. The inclusion phase of the 5th study ran from 2011 to 2015. Participants were randomly invited citizens of the greater Copenhagen area between ages 20 to 99. All participants gave written informed consent. The Copenhagen City Heart Study was conducted in accordance with the second Helsinki Declaration and approved by the regional ethics committee.

In this echocardiographic substudy, all 4,466 participants were invited to receive an echocardiographic examination independently of health status. Inclusion criteria were age ≥ 18 years and the ability to cooperate to an echocardiographic examination. Exclusion criteria were insufficient image quality for 2DSTE analysis (N = 334), non-sinus rhythm during echocardiography (N = 41), and prevalent heart failure at baseline (N = 92). Hence, a total of 453 participants were excluded resulting in a final study population of 4,013 participants.

Health Examination and baseline information.

All participants answered an extensive self-administered questionnaire and underwent a thorough health examination. Health examination was conducted by the same method as in the 4th study of the Copenhagen City Heart Study as described previously⁸. In brief, hypertension was defined as a mean systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medication. Hypercholesterolemia was defined as an LDL blood concentration above ≥ 3.0 mmol/L or use of cholesterol-lowering medication. Diabetes was defined by use of diabetes medication, insulin therapy, or self-reported disease. The above-mentioned diagnoses were supplemented by use of ICD-10 and ICD-8 codes obtained from the Danish National Patient

Registry. Diagnosis of heart valve disease (mitral and aortic stenosis and regurgitation) or history of ischemic heart disease (stable angina pectoris, acute myocardial infarction, coronary intervention, percutaneous coronary intervention, and coronary artery by-pass grafting) was obtained through the same methods. Participants were classified into ACC/AHA stages of HF⁹ according to their data at baseline. Participants were designated as stage A HF if they suffered from hypertension, diabetes mellitus, or coronary artery disease (besides myocardial infarction). Participants with a history of previous myocardial infarction, LV hypertrophy, LV dilatation, abnormal LV ejection fraction (defined according to current guidelines¹⁰), or valvular heart disease were classified as stage B.

Follow-up and outcome

The primary outcome was a composite outcome of incident HF or CVD. Follow-up was 100%. Information regarding outcome was obtained through the Danish National Patient Registry and the National Danish Cause of Death Registry utilizing ICD-10 codes. Use of ICD-10 from Danish registries has previously been validated. ICD-10 codes of HF were demonstrated to have a positive predictive value of 100 % when clinically assessed ¹¹.

Echocardiography

Echocardiographic examinations were conducted using Vivid 9 ultrasound systems (GE Healthcare, Horten, Norway) and performed by experienced sonographers following a predetermined protocol. All images were stored in a GE Healthcare image vault and analyzed by a single experienced investigator with Echopac version 113.1.5 (GE Healthcare, Horten, Norway).

Conventional Echocardiography

All conventional echocardiographic measurements were performed according to existing guidelines^{10,12}. Abnormal LV ejection fraction was defined as < 54% for females and < 52% for males. LV hypertrophy was defined as LV mass index ≥ 96 g/m² or ≥ 116 g/m² for females and

males respectively. Relative wall thickness was calculated as $2 * \text{posterior wall thickness} / \text{LV internal diameter at end-diastole}^{10}$. Global peak systolic tissue velocity was assessed by color tissue Doppler echocardiography by averaging the peak systolic tissue velocity measured with a sample placed basal segment in the two LV wall of each view. Conventional echocardiography analysis in the 5th Copenhagen City Heart Study have previously been described in detail¹³.

Two-Dimensional Speckle Tracking Echocardiography

2DSTE analysis was conducted in apical 4-chamber, 2-chamber, and long-axis view focused on the LV. Images were optimized for 2DSTE analysis of the LV by adjusting depth and sector width to clearly visualize the myocardium of the LV. Average frame rate per second was 63.1 ± 6.1 optimal for 2DSTE analysis. LV myocardium was tracked with a semi-automated function outlining a region of interest spanning from the endomyocardial to the epimyocardial borders. Region of interest could be adjusted by the investigator if deemed necessary. The LV was divided into 6 segments in each view and was excluded from further analysis by the investigator if speckle tracking was inadequate or segments were disturbed by image artifacts. GLS_{sw} , GLS_{Endo} , and GLS_{Epi} were calculated from the peak systolic values of each segment. All GLS measurements are reported as absolute values. Inter- and inter-observer reproducibility of GLS-parameters was assessed in 20 randomly selected participants. Both investigators were blinded. The repeated 2DSTE analysis was performed more than 1 year following the original measurements. Absolute biases (mean difference \pm 1.96 SD) and ICC were assessed. Lower reference limits of layer-specific GLS were based on a previous study on sex-based layer-specific normal values¹⁴. Abnormal GLS_{sw} was defined as $<16.6\%$ for females and $<15.1\%$ for males. Abnormal GLS_{Endo} was defined as <19.4 for females and $<17.8\%$ for males. Finally, abnormal GLS_{Epi} was defined as $<14.2\%$ for females and $<13.0\%$ for males.

Statistical Analysis

STATA statistics/data analysis, SE 15.0 (StataCorp, College Station, TX, USA) was used for all data work. Statistical significance was defined as a P-value <0.05. Baseline characteristics were compared between the group reaching the composite outcome and the group who did not using student's T-test, Wilcoxon Rank-Sum test/Kruskal-Wallis test, Chi²-test for respectively Gaussian distributed continuous variables, non-Gaussian continuous variables, and categorical variables. Gaussian continuous variables were reported as mean values \pm standard deviation, non-Gaussian continuous variables as median along with interquartile range, and categorical variables as frequencies and percentages. Restricted cubic spline curves were constructed to test the predictive value of GLS_{sw}, GLS_{Endo}, and GLS_{Epi} using a Poisson model to estimate incidence rates. The number of knots was chosen according to the Akaike information criterion. To test the prognostic value of GLS_{sw}, GLS_{Endo} and GLS_{Epi}, Cox proportional hazard regression analysis was utilized. Both univariable and multivariable Cox regressions were performed. Three multivariable models were constructed. Model 1 included sex, age, body mass index, number of pack-years, physical activity level in leisure time, creatinine blood concentration, hypertension, hypercholesterolemia, and diabetes. In model 2, the echocardiographic parameters LV mass and LV ejection fraction were added to the variables included in model 1. Model 3 included the variables of model 1 and 2 as well as history of ischemic heart disease and valvular heart disease. For supplementary analysis, the prognostic value of cut-offs of conventional echocardiographic measurements were assessed with model 3. Furthermore, a holistic scoring system was created based on the number of abnormal findings (of the conventional measurements in addition to each layer-specific parameter) significantly associated with HF and/or CVD. Test for collinearity for all models were performed. Finally, incremental model performance of GLS_{sw}, GLS_{Endo}, or GLS_{Epi} was investigated using reclassification analysis. Continuous net reclassification improvement (NRI) was assessed when adding a GLS parameter to the widely used clinical risk models SCORE risk chart¹⁵ (age, total cholesterol levels, systolic blood pressure, and

smoking status (active vs previous/never)) and the Framingham Risk Score¹⁶ (age, total cholesterol levels, HDL concentration, systolic blood pressure, use of antihypertensive medication, smoking status (active vs previous/never), and diabetes mellites). NRI for each parameter stratified by sex was illustrated in a forest plot. Pearson's r was investigated to assess the correlation between conventional echocardiographic measurements and GLS parameters in unstratified and sex-stratified analysis.

Results

Baseline Characteristics

A total of 4,013 members of the general population were included in this study. Individuals included were generally younger and were less comorbid than participants excluded due to insufficient image quality for speckle tracking analysis (n=334) (Supplementary Table 1). Mean age of the study cohort was 56 years and 57% were female. Mean GLS parameter values were 19.4% for GLS_{sw}, 22.9% for GLS_{Endo}, and 16.8% for GLS_{Epi}. At baseline a total of 1478 (37%) was free of both clinical HF risk factors and structural heart disease, meanwhile 1185 (30%) had stage A HF, and 1350 (34%) had stage B HF. Of those free of HF risk factors and structural heart disease only 20 (1%) had a GLS_{sw} (14 for GLS_{Endo}, 18 for GLS_{Epi}) below the lower limit of normality. GLS_{sw} was abnormal in 36 (3%) in the stage A HF group (30 for GLS_{Endo}, 36 for GLS_{Epi}) and in 223 (17%) in the stage B HF group (223 for GLS_{Endo}, 212 for GLS_{Epi}).

Median follow-up was 3.5 years [IQR: 2.6-4.3 years]. During follow-up 133 participants (3.3%) (55 females and 78 males) met the composite outcome. A total of 101 (2.5%) (37 females and 64 males) developed HF and 45 (1.1%) (22 females and 23 males) suffered CVD. All baseline characteristics of the study cohort are displayed in **Table 1**. GLS_{sw} ($18.6 \pm 2.4\%$ vs $20.0 \pm 2.3\%$, $P < 0.001$), GLS_{Endo} ($22.0 \pm 2.8\%$ vs $23.6 \pm 2.8\%$, $P < 0.001$), and GLS_{Epi} (16.13 ± 2.1 vs $17.4 \pm 2.1\%$, $P < 0.001$) were all significantly lower in males compared to females. See **Supplementary Table 2** for baseline characteristics stratified by sex.

GLS_{sw}, GLS_{Endo}, and GLS_{Epi} were significantly reduced in participants developing HF and/or CVD. Participants suffering the composite outcome were also significantly older, more likely to be male, had fewer years of education, participated in less physical activities during leisure time, smoked more, had higher body mass index, systolic and diastolic blood pressures. They also suffered more frequently from hypertension, hypercholesterolemia, diabetes, valve disease, ischemic heart disease,

and had higher blood concentration levels of creatinine and glucose. Finally, LV mass index, relative wall thickness, E/e', and left atrial volume index were significantly elevated while LV ejection fraction and E/A were significantly reduced in the sample who reached the outcome. (**Table 1**). Impaired LV ejection fraction, global peak systolic tissue velocity, E/e', E/A, left atrial volume index, and LV mass index were all correlated with impaired layer-specific GLS (Supplementary Table 3).

Reproducibility

For GLS_{sw}, intra-observer variability was $-0.1 \pm 2.3\%$ (ICC=0.96), and inter-observer variability was $0.3 \pm 2.7\%$ (ICC=0.94). Intra-observer variability of GLS_{Endo} was $-0.3 \pm 2.7\%$ (ICC=0.95), while inter-observer variability was $0.2 \pm 2.7\%$ (ICC=0.95). For GLS_{Epi}, intra-observer variability was found to be $-0.1 \pm 1.8\%$ (ICC=0.96) while inter-observer variability was $0.4 \pm 2.2\%$ (ICC=0.96). Sex-stratified reproducibility analyses are displayed in **Supplementary Table 4**.

Relationship between layer-specific GLS and outcome

Univariable and multivariable Cox regressions for all models are displayed in **Table 2**. In univariable survival analysis, all GLS parameters (GLS_{sw}: Hazard ratio (HR)=1.41, 95% CI [1.34;1.48], per 1% decrease) (GLS_{Endo}: HR=1.32, 95% CI [1.27;1.39], per 1% decrease) (GLS_{Epi}: HR=1.47, 95% CI [1.39;1.56], per 1% decrease) were significantly associated with future incident HF and/or CVD. All GLS parameters remained significant when stratified by sex in univariable regressions, however, the prognostic value of GLS seemed stronger in males than females. Sex was found to significantly modify the relationship between outcome and GLS_{sw} (P for interaction = 0.014), GLS_{Endo} (P for interaction = 0.014), and GLS_{Epi} (P for interaction = 0.018). Incidence rate of HF and/or CVD was significantly higher in males compared to females when GLS parameters were abnormal (**Supplementary table 5**).

All 3 GLS parameters remained significant when adjusting for demographic, clinical, and

biochemistry parameters of model 1 in unstratified and sex-stratified analysis (**Table 2**). After adding echocardiographic measurements and prevalent ischemic and valvular heart disease to the multivariable model, all GLS parameters remained as independent predictors of the composite outcome of HF and/or CVD. Supplementary Table 6 lists the association between cut-off values of conventional echocardiographic parameters and HF and/or CVD. The distribution and overlap of the cut-off values of conventional echocardiographic parameters and abnormal GLS parameters are depicted Venn diagrams in addition to the incidence rate of HF and/or CVD according to the holistic score system (Supplementary Figure 1). In sex stratified analysis, no layer-specific GLS parameter was found to be significantly associated with outcome in females. In males GLS_{WW} (HR=1.16, 95%CI [1.02;1.31], per 1% decrease) and GLS_{Epi} (HR=1.19, 95%CI [1.04;1.38], per 1% decrease) were found to be independent predictors of HF and/or CVD. GLS_{WW} and GLS_{Epi} remained significantly associated with the composite outcome, when restricting the analysis to participants without previous ischemic heart disease and valvular heart disease in males (**Table 2**). No collinearity was observed in any of the regression models. In restricted cubic spline curves, the relationships between GLS_{WW}, GLS_{Endo}, GLS_{Epi}, and HF and/or CVD in the whole cohort and stratified by sex are illustrated (**Figure 1**).

Finally, there was a significant discrepancy between the two sexes when assessing the incremental prognostic value of GLS parameters. In reclassification analysis, all GLS parameters provided incremental prognostic information in males, both when added to the SCORE risk chart and the Framingham Risk model. No GLS parameter provided a significant increase in NRI in females (**Figure 2**). These findings did not change, when restricting analysis to participants without diabetes mellitus or previous ischemic heart disease.

Discussion

In the present report we included 4,013 citizens amongst who 133 reached our composite outcome of HF and/or CVD during a follow-up period of median 3.5 years. GLS_{sw}, GLS_{Endo}, and GLS_{Epi} were all associated with HF and/or CVD after multivariable adjustment. However, sex was found to significantly modify the relationship between all GLS parameters and outcome. In sex stratified analysis, GLS_{sw} and GLS_{Epi} were found to be the only significant predictor after multivariable adjustments in males. These results remained unchanged when including LV ejection fraction, LV mass index, prevalent ischemic heart disease or cardiac valve disease in multivariable regression models. Finally, only in males did layer-specific GLS parameters provide incremental prognostic information to well established general population risk models.

GLS_{sw} measured with EchoPac software is calculated as the mean longitudinal strain between the inner and outer border of the region of interest. GLS_{Endo} and GLS_{Epi} are derived from an inner and outer layer of the region of interests. The total width of these two layers is narrower than the original region of interest for whole wall strain. Consequently, even though we also found that GLS_{sw} remained a significant predictor in model 3, it is likely that the prognostic value of GLS_{sw} mostly is driven by GLS_{Epi}, since GLS_{Endo} was not significantly associated with the outcome.

This may not be the expected finding when considering the pathophysiology of the ailing heart. Studies have shown the longitudinal orientated myocardial fibers of the endomyocardium to be the most sensitive particularly to ischemia^{17,18}. Thus, it seems unlikely that the discrepancy in prognostic value of layer-specific GLS has a biological explanation but rather a technical. We believe the echocardiography-perceived quantification of myocardial longitudinal deformation of the epimyocardial layer may correlate more closely to the actual myocardial status, than that measured in the endomyocardial layer. We have previously found the reproducibility of GLS_{Epi} to be superior to GLS_{Endo}¹⁹. We found intra- and inter-observer variability to be slightly better for GLS_{Epi} (Intra-

observer variability: $0.1 \pm 1.8\%$, ICC = 0.96. Inter-observer variability: $0.4 \pm 2.2\%$, ICC = 0.96), as compared to GLS_{Endo} (Intra-observer variability: $-0.3 \pm 2.7\%$, ICC = 0.95. Inter-observer variability: 0.2 ± 2.7 , ICC = 0.95), however the difference was minimal. Thus, this factor may not be the only explanation for the results presented in the current report. Several other factors could affect the validity of the quantification of longitudinal deformation in the endomyocardial layer compared to the epimyocardial layer. The endomyocardial 2DSTE region of interest may be more difficult to outline precisely to only contain myocardial tissue as the endocardial border generally has a more varied contour. Additionally, apical foreshortening has been shown to severely affect longitudinal strain²⁰. This may affect apical endomyocardium longitudinal strain more compared to the apical epimyocardium as the epimyocardial part is less evasive. Finally, regional longitudinal strain of the epimyocardium has been demonstrated to be significantly more homogenous than that of regional endomyocardial longitudinal strain, which varies far more from the apical to basal level²¹.

Another finding of the present study was the effect modification of layer specific GLS by sex. We found GLS_{Epi} (and GLS_{sw}) to be a strong and independent predictor of the composite outcome in males, while no GLS parameter was significantly associated with outcome in females (**Table 2, Figure 1**). None of the aforementioned studies investigating the prognostic value of layer-specific GLS assessed whether sex modified the association. However, a study by Reimer Jensen et al²² investigated the prognostic value of GLS_{sw} in regards to the development of HF in 4960 participants of Atherosclerosis Risk in Communities (ARIC) study. The authors reported that they did not observe any effect modification by sex. But there are several key differences between these two studies, which may explain the different findings. The study sample of ARIC is significantly older (mean age 75 years \pm 5 vs 56 years \pm 18 years) with a narrower age distribution. Furthermore, the frequency of comorbidities is considerably higher (obesity: 32.2% vs 12.9%, hypertension: 80.8% vs 49.9%, diabetes: 34% vs 4.6%, ischemic heart disease: 10% vs 6.2%). Also, the ARIC study utilized different ultrasound systems and vendor-dependent software. Finally, the

echocardiograms of the ARIC study were of substantially lower frame rate limiting the temporal resolution. The incidence rate of the composite outcome was significantly lower in females compared to males (55 (2.4%) vs 78 (4.5%), $P < 0.001$). This may partly explain the sex-specific difference in prognostic value of GLS parameters. However, our lab has previously found that sex modified the relationship between GLS_{sw} and a combined outcome of acute myocardial infarction, HF, and CVD (and HF alone) in the general population of the 4th Copenhagen City Heart Study³ (2001-2003) (n=1296 and 58% females: 72 (13.1%) and 77 (10.3%) adverse composite events in males and females respectively). The main differences between the 4th and 5th Copenhagen City Heart Study are the substantially larger sample size, significantly improved image quality of the recorded echocardiograms, and more developed post-processing software with lower inter-vendor variability²³. Furthermore, the study by Biering-Sørensen et al did not unfortunately assess the reproducibility of GLS (neither sex-stratified) or the correlation between GLS and conventional echocardiographic parameters. Likewise, our lab has also reported a similar sex modification of the prognostic value of GLS_{sw} and all-cause death in HF patients² (n=1065 and 26% females: 136 (17.5%) and 41 (16.4%) adverse events in males and females respectively). Both studies found GLS_{sw} to be an especially strong prognosticator in males as compared to females. Thus, the present study further validates that the prognostic value is significantly modified by sex regarding the development of adverse cardiovascular outcome. It appears unlikely that the difference in incidence rates may provide the sole explanation for our findings, since the current observation of differential prognostic utility of GLS between genders now has been observed in 3 independent cohorts, and these studies are amongst the largest studies investigating the prognostic value of GLS. We did not observe any difference in association between GLS_{Epi} or GLS_{sw} with other systolic markers in the present study (**Supplementary Table 3**). Thus, different associations between GLS-parameters and systolic measurements across genders do not explain the discrepancy in prognostic information. A potential reason why GLS_{Epi} was found to be a superior prognosticator in males as compared to

females could potentially be due to the measure being less reproducible in females as compared to males as demonstrated in **Supplementary Table 4**. This may be explained by men having higher larger with larger LV mass than women²⁴, thus men have a larger LV wall area (and therefore a higher number of speckles) to track with 2DSTE. Additionally, the effect modification of sex could be caused by sex-specific pathophysiological LV remodeling. Previous studies have demonstrated that women are more likely to develop concentric remodeling and diastolic dysfunction, while they are more often observed to have preserved systolic function (both with and without cardiovascular diseases).^{25,26} The different course of LV remodeling between sexes may be related to several humoral factors²⁷. Consequently, echocardiographic markers of systolic function may not be as sensitive early markers of cardiovascular disease in females compared to males. This is further supported by the findings of Lundorff et al, who found LV mass index and e' to be significant independent predictors of cardiovascular outcome in women in the 4th Copenhagen City Heart Study, where GLS_{sw} was not²⁸. Additionally, all GLS parameters were significant predictors of HF and/or CVD in females in model 1 before adjustment for echocardiographic parameters, which included LV mass (**Table 2**). Finally, we assessed the impact of the cardiovascular risk factors on changes in GLS_{sw} during a 10-year period between the 4th and 5th Copenhagen City Heart Study, which included 689 participants who had GLS_{sw} measured at both timepoints¹³. We found that male sex was independently associated with an accelerated decrease of GLS as the heart aged. This further supports that GLS parameters may be more susceptible to pathophysiologic changes in males than females.

The results of the present study indicate that GLS_{Epi} is the most valuable GLS parameter entailing important prognostic information in males primarily. The authors suggest that GLS_{Epi} correlates more closely to the actual systolic function than that of GLS_{sw} and GLS_{Endo}. Thus, the present results might indicate that GLS_{Epi} should be considered as the GLS measure of choice to be included in clinical risk stratification of males. Evaluating GLS_{Epi} instead of GLS_{sw} in newly referred

patients in outpatient clinics may facilitate improved early risk intervention before further myocardial impairment is present, ultimately resulting in reduced cardiovascular morbidity and mortality. However, the authors believe it is too early to recommend the use of GLS_{Epi} over GLS_{ww} in the clinical evaluation of low-risk patients from the general population as this is the first study assessing the usefulness of these parameters in a general population. Meanwhile, GLS parameters may not entail valuable prognostic information in women. Consequently, these results should be validated in other prospective cohorts, as our findings could potentially influence how GLS parameters are utilized in males and females.

Strengths and limitations

A significant strength of the present prospective study is the complete follow-up and the large cohort size based on a homogenous population sample spanning across all adult ages for both sexes. Additionally, only one single and experienced investigator analyzed all echocardiograms and only utilized one single version of echocardiographic software, minimizing measurement variability. It is important to stress that the findings of the present study suffer from a degree of selection bias as participants with sufficient image quality for speckle tracking were younger and less comorbid than participants with insufficient image quality. This may limit the generalizability of the results. There may be some concerns regarding overfitting of the sex-stratified Cox proportional hazard models especially in the stratified analysis. However, Vittinghoff et al²⁹ demonstrated in several simulation studies that the rule of thumb of minimum 10 events per predictor variable in Cox regression models could be stretched particularly when using models to demonstrate adequate control of confounding. Finally, the generalizability of our results to study samples analyzed with different echocardiographic hardware and software may not be feasible as the EACVI-ASE Strain Standardization Task Force has demonstrated inter-vendor differences for GLS_{Endo} to be considerable³⁰. Additionally, inter-vendor bias for GLS_{Epi} has yet to be assessed.

Conclusion

Sex modified the relationship between all GLS parameters and outcome in the general population. Consequently, GLS_{Epi} was found to be the only layer-specific GLS parameter to be an independent predictor of HF and/or CVD in males. No GLS parameter provided independent prognostic information in females. Finally, GLS parameters only provided incremental prognostic information to conventional risk models in males.

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Conflicts of interest

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Figure legends

Figure 1: Title: Incidence rate of incident HF and/or CVD according to GLS_{SW}, GLS_{Endo}, and GLS_{Epi}.

Caption: Restricted cubic spline curves illustrating incidence rate per 1000 patient-years of HF and/or CVD according to GLS_{SW}, GLS_{Endo}, and GLS_{Epi} in the whole cohort and in subgroup analysis of males and females. P-value for interaction and 95% confidence intervals are included.

Abbreviations: HF (heart failure), CVD (cardiovascular death), GLS_{SW} (whole wall global longitudinal strain), GLS_{Endo} (endomyocardial global longitudinal strain), GLS_{Epi} (epimyocardial global longitudinal strain).

Figure 2: Title: Incremental prognostic information of GLS_{SW}, GLS_{Endo}, and GLS_{Epi}.

Caption: Forest plot displaying continuous NRI when adding GLS_{SW}, GLS_{Endo} or GLS_{Epi} to the SCORE risk model or Framingham risk model stratified by sex. 95% confidence intervals are included.

Abbreviations: NRI (net reclassification improvement), GLS_{SW} (whole wall global longitudinal strain), GLS_{Endo} (endomyocardial global longitudinal strain), GLS_{Epi} (epimyocardial global longitudinal strain), 95%CI (95% confidence intervals).

Table 1. Baseline characteristics.

	Whole study cohort (n = 4013)	No HF and/or CVD (n = 3880)	Development of HF and/or CVD (n = 133)	P-value
Demographics				
Female sex, n (%)	2290 (57.1)	2235 (57.6)	55 (41.4)	<0.001
Age, years	56.2 ± 17.5	55.5 ± 17.3	75.5 ± 10.0	<0.001
Years of education, years	12 [10; 13]	12 [10; 13]	10 [7; 12]	<0.001
Physical activity level in leisure time				
Sedentary, n (%)	286 (7.2)	270 (7.0)	16 (12.6)	<0.001
Low, n (%)	1531 (38.7)	1464 (38.2)	67 (52.8)	
Moderate, n (%)	1813 (45.8)	1776 (46.3)	37 (29.1)	
High, n (%)	330 (8.3)	323 (8.4)	7 (5.5)	
Clinical data				
Body mass index, kg/m ²	25.4 ± 4.2	25.4 ± 4.2	26.6 ± 4.6	0.002
Systolic blood pressure, mmHg	137.7 ± 20.7	137.4 ± 20.6	147.8 ± 22.2	<0.001
Diastolic blood pressure, mmHg	78.7 ± 10.6	78.8 ± 10.6	77.6 ± 12.1	0.23
Hypertension, n (%)	2001 (49.9)	1889 (48.7)	112 (84.2)	<0.001
Hypercholesterolemia, n (%)	2488 (62.0)	2388 (61.5)	100 (75.2)	0.001
Diabetes, n (%)	183 (4.6)	160 (4.1)	23 (17.3)	0.001
Previous ischemic heart disease, n (%)	249 (6.2)	214 (5.5)	35 (26.3)	<0.001
Cardiac valve disease, n (%)	32 (0.8)	24 (0.6)	8 (6.0)	<0.001
Stage A/B HF				
Not at risk, no structural heart disease, n (%)	1478 (36.8)	1471 (37.9)	7 (5.3)	<0.001
Stage A, n (%)	1185 (29.5)	1150 (29.6)	35 (26.3)	
Stage B, n (%)	1350 (33.6)	1259 (32.4)	91 (68.4)	
Smoking status				
Active smoker, n (%)	700 (18.5)	668 (18.3)	32 (25.8)	0.018
Previous smoker, n (%)	1561 (41.3)	1505 (41.2)	56 (45.2)	
Never smoked, n (%)	1516 (40.1)	1480 (40.5)	36 (29.0)	
Pack years, 12.5 g tobacco/day x years smoked	0.3 [0; 13.2]	0.3 [0; 12.5]	7.5 [0; 33.1]	<0.001
Biochemistry				
Glucose, mmol/L	5.4 ± 1.2	5.4 ± 1.2	5.7 ± 1.2	0.004
LDL cholesterol, mmol/L	3.1 ± 1.0	3.1 ± 1.0	3.1 ± 1.1	0.82
HDL cholesterol, mmol/L	1.6 ± 0.5	1.6 ± 0.5	1.6 ± 0.5	0.20
Creatinine μmol/L	76.5 ± 13.4	78.3 ± 13.0	82.8 ± 20.1	<0.001
Hemoglobin, mmol/L	8.8 ± 0.7	8.8 ± 0.7	8.7 ± 0.8	0.18
Echocardiography				
LV mass index, g/m ²	82.6 [71.0; 96.7]	82.2 [70.8; 95.9]	98.9 [78.7; 114.5]	<0.001
LV hypertrophy, n (%)	548 (13.9)	499 (13.1)	49 (37.7)	<0.001
Relative wall thickness	0.40 ± 0.09	0.40 ± 0.09	0.44 ± 0.11	<0.001
E/e'	7.0 [5.6; 9.0]	6.9 [5.6; 8.9]	10.1 [8.0; 13.7]	<0.001
E/e' > 14, n (%)	121 (3.2)	98 (2.7)	23 (22.1)	<0.001

LV ejection fraction, %	56.6 ± 6.0	56.8 ± 5.8	50.3 ± 8.9	<0.001
E/A-ratio	1.25 ± 0.52	1.26 ± 0.52	0.95 ± 0.43	<0.001
Left atrium volume index, mL/m ²	24.4 ± 8.3	24.1 ± 8.0	30.8 ± 13.4	<0.001
Left atrial volume index >34 mL/m ² , n (%)	415 (10.4)	379 (9.8)	36 (27.1)	<0.001
GLS _{ww} , %	19.4 ± 2.4	19.5 ± 2.3	16.8 ± 4.0	<0.001
Frequency of abnormal GLS _{ww} , %	279 (7.0)	227 (5.9)	52 (39.1)	<0.001
GLS _{Endo} , %	22.9 ± 2.9	23.0 ± 2.7	19.9 ± 4.7	<0.001
Frequency of abnormal GLS _{Endo} , %	267 (6.7)	216 (5.6)	51 (38.3)	<0.001
GLS _{Epi} , %	16.8 ± 2.2	16.9 ± 2.1	14.6 ± 3.5	<0.001
Frequency of abnormal GLS _{Epi} , %	266 (6.6)	218 (5.6)	48 (36.1)	<0.001

LV (left ventricular), E/e' (Ratio of peak early transmitral filling velocity to peak early diastolic tissue velocity), GLS_{ww} (whole wall global longitudinal strain), GLS_{Endo} (endomyocardial global longitudinal strain), GLS_{Epi} (epimyocardial global longitudinal strain)

Table 2.

Univariable and multivariable Cox proportional hazard regressions investigating the prognostic value of layer-specific GLS parameters.

	<u>Univariable regression</u>			<u>Model 1</u>			<u>Model 2</u>			<u>Model 3</u>		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-Value	HR	95% CI	P-Value
<u>Whole cohort (n=4013)</u>												
GLS _{WW} , per 1% decrease	1.41	1.34;1.48	<0.001	1.26	1.19;1.34	<0.001	1.15	1.05;1.25	0.002	1.15	1.05;1.25	0.002
GLS _{Endo} , per 1% decrease	1.33	1.27;1.39	<0.001	1.21	1.15;1.27	<0.001	1.10	1.03;1.19	0.007	1.10	1.02;1.19	0.009
GLS _{Epi} , per 1% decrease	1.47	1.39;1.56	<0.000	1.30	1.21;1.39	<0.001	1.18	1.07;1.29	0.001	1.18	1.07;1.30	0.001
<u>Females (n=2290)</u>												
GLS _{WW} , per 1% decrease	1.31	1.21;1.42	<0.001	1.15	1.03;1.28	0.010	1.11	0.97;1.27	0.14	1.10	0.96;1.27	0.16
GLS _{Endo} , per 1% decrease	1.24	1.15;1.34	<0.001	1.11	1.02;1.22	0.017	1.07	0.95;1.20	0.24	1.07	0.95;1.20	0.28
GLS _{Epi} , per 1% decrease	1.36	1.24;1.49	<0.001	1.17	1.04;1.32	0.013	1.14	0.98;1.32	0.10	1.13	0.97;1.32	0.11
<u>Males (n=1723)</u>												
GLS _{WW} , per 1% decrease	1.49	1.39;1.60	<0.001	1.32	1.22;1.42	<0.001	1.14	1.01;1.29	0.028	1.16	1.02;1.31	0.024
GLS _{Endo} , per 1% decrease	1.39	1.31;1.47	<0.001	1.25	1.17;1.33	<0.001	1.10	0.99;1.21	0.067	1.10	0.99;1.22	0.058
GLS _{Epi} , per 1% decrease	1.57	1.45;1.70	<0.001	1.37	1.26;1.50	<0.001	1.18	1.03;1.35	0.017	1.19	1.04;1.38	0.014

GLS_{WW} (whole wall global longitudinal strain), GLS_{Endo} (endomyocardial global longitudinal strain), GLS_{Epi} (epimyocardial global longitudinal strain)

Model 1 included variables sex (omitted from subgroup analysis), age, BMI, pack years, physical activity level in leisure time, creatinine blood concentration, hypertension, hypercholesterolemia, and diabetes.

Model 2 included variables of model 1 in addition to LV mass and LV ejection fraction.

Model 3 included the variables of model 1 and 2 in addition to prevalent ischemic heart disease and valvular heart disease.

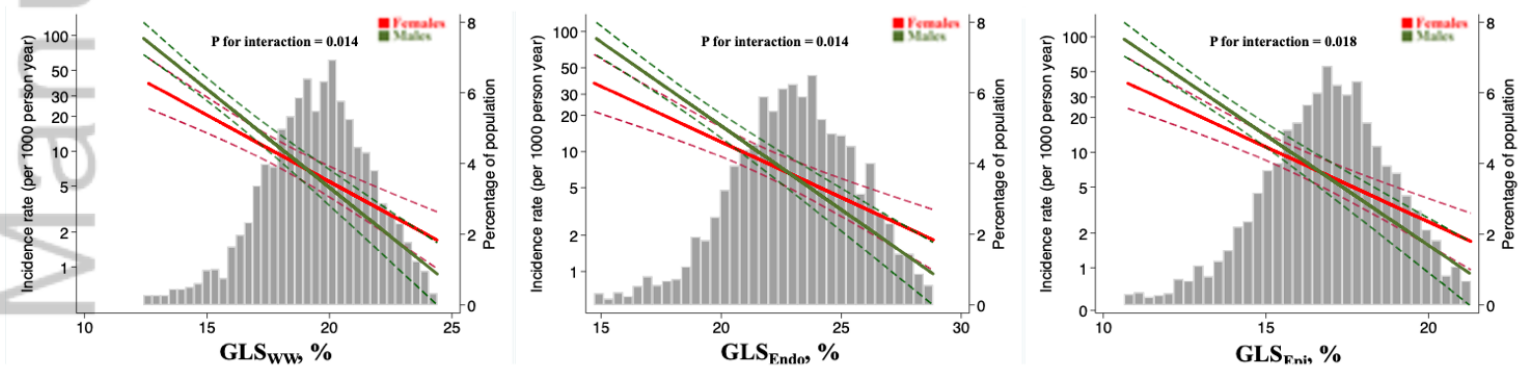


Figure 1.tiff

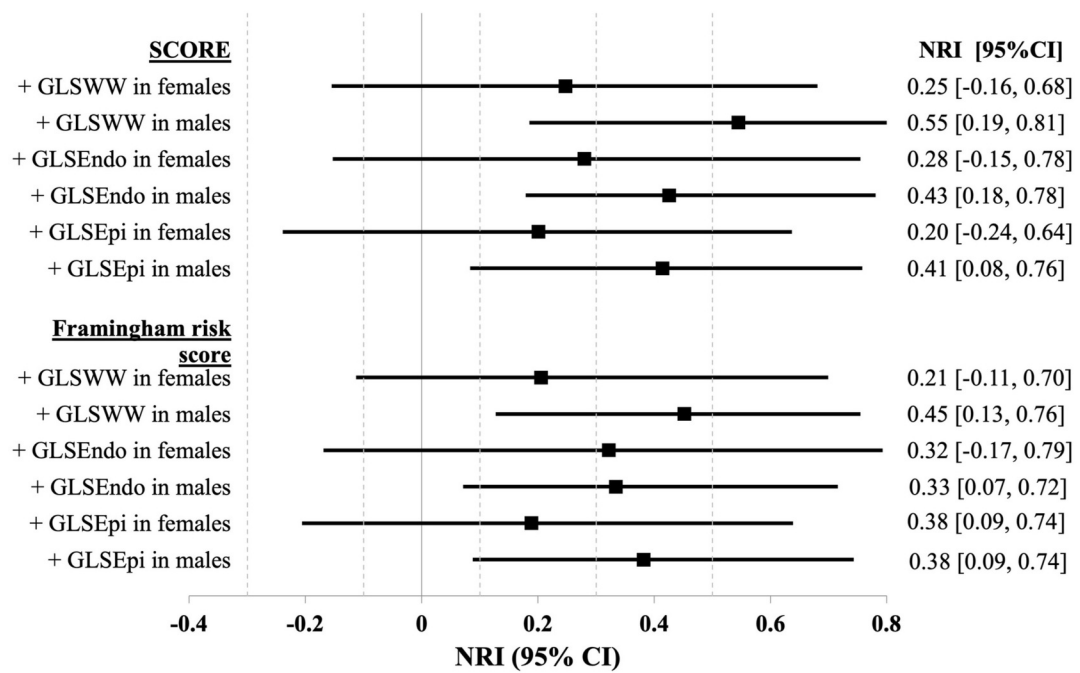


Figure 2.jpg

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