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## Left Ventricular Global Function Index By Magnetic Resonance Imaging- A Novel Marker for Assessment of Cardiac Performance for the Prediction Of Cardiovascular Events: The Multi-Ethnic Study of Atherosclerosis

Nathan Mewton, MD, PhD<sup>1,7,\*</sup>, Anders Opdahl, MD<sup>1,8,\*</sup>, Eui-Young Choi, MD, PhD<sup>1</sup>, Andre L. C. Almeida, MD<sup>1</sup>, Nadine Kawel, MD<sup>6</sup>, Colin O. Wu, PhD<sup>2</sup>, Gregory L. Burke, MD, MS<sup>3</sup>, Songtao Liu, PhD<sup>5</sup>, Kiang Liu, PhD<sup>4</sup>, David A. Bluemke, MD, PhD<sup>5</sup>, and Joao A. C. Lima, MD<sup>1</sup>

<sup>1</sup>Department of Medicine, Division of Cardiology, School of Medicine, Johns Hopkins University, Baltimore, MD

<sup>2</sup>National Heart, Lung, and Blood Institute, Bethesda, MD

<sup>3</sup>Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC

<sup>4</sup>Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL

<sup>5</sup>National Institute for Biomedical Imaging and Bioengineering, Bethesda, MD

<sup>6</sup>Radiology and Imaging Sciences, National Institutes of Health, Bethesda, MD

<sup>7</sup>Centre d'Investigation Clinique de Lyon, Hôpital Cardiovasculaire Louis Pradel, Lyon, France

<sup>8</sup>Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway

### Abstract

LV function is generally assessed independent of structural remodeling and vice versa. The purpose of this study was to evaluate a novel LV global function index (LVGFI) that integrates LV structure with global function and to assess its predictive value for cardiovascular (CV) events throughout adult life in a multi-ethnic population of men and women without history of cardiovascular diseases at baseline. A total of 5004 participants in the Multi-Ethnic Study of Atherosclerosis underwent a cardiac magnetic resonance (CMR) study and were followed up for a median of 7.2 years. The LVGFI by CMR was defined by the ratio of stroke volume divided by LV total volume defined as the sum of mean LV cavity and myocardial volumes. Cox proportional hazard models were constructed to predict the end points of heart failure (HF), hard CV events and a combined endpoint of all CV events after adjustment for established risk factors, calcium score and biomarkers. A total of 579 (11.6%) incident events were observed during the follow-up period. In adjusted models, the end points of HF, hard CV events and all events were all significantly associated with LVGFI (HF, hazard ratio [HR]= 0.64,  $p < 0.0001$ ; hard CV events,

Corresponding author: Joao A.C. Lima, MD, FACC, Professor of Medicine and Radiology, Johns Hopkins Hospital, 600 North Wolfe Street, Blalock 524D1, Baltimore, MD 21287, Telephone : (410) 614-1284 / Fax : (410) 614-8222, jlima@jhmi.edu.

\*Anders Opdahl and Nathan Mewton have equally contributed to this work.

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HR=0.79, p=0.007; all events, HR=0.79, p<0.0001). LVGFI had a significant independent predictive value in the multivariable models for all CV event categories. The LVGFI was a powerful predictor of incident heart failure, hard CV events and a composite endpoint including all events in this multiethnic cohort.

## Keywords

left ventricle; ejection fraction; heart failure; LV mass; LV global function index

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## Introduction

Left ventricular function must be sufficient for adequate oxygen delivery to peripheral organs and tissues. In varying physiological conditions, this is accomplished by modulating heart rate and/or stroke volume (SV) through several mechanisms. The short-term regulation of SV involves changes in preload, afterload and contractility, whereas intermediate- and long term regulation include physiologically and/or pathologically mediated left ventricular (LV) remodeling.<sup>1</sup> In pathological situations, this remodeling may affect the LV passive-elastic properties, myocardial mass, and LV chamber size.<sup>2</sup> Therefore, the relationship between SV and LV size may carry information about physiological as well as pathological remodeling.

The most frequently used index of LV function in clinical practice<sup>3,4</sup>, the LV ejection fraction (LVEF), does not account for the relationship between LV mass and LV dimensions. This might partly explain its limited sensitivity and specificity in various stages of cardiovascular (CV) diseases.<sup>3,5,6</sup> Furthermore, in spite of being an established marker of LV systolic function, LVEF fails to index diastolic dysfunction.<sup>7,8</sup> Recently, other LV parameters such as the LV mass normalized for body size and LV end-diastolic mass/volume ratio (LVMVR) have been shown to be independently associated with cardiovascular outcome.<sup>9-12</sup>

As stroke volume will vary with heart size in healthy individuals, a relationship between SV and total heart size including the LV mass and overall LV cavity size (mean of end-diastolic and end-systolic volumes) can be predicted. Patients with congestive heart failure (CHF) due to LV systolic dysfunction (LVEF<50%)<sup>13</sup> frequently have LV dilation with preserved SV at least initially, before progressive systemic decompensation.<sup>14</sup> On the other hand, CHF patients with predominant diastolic dysfunction typically have preserved LVEF with smaller LV cavities and thicker walls.<sup>14,15</sup> Indeed, as previously demonstrated, relationships between SV and LV cavity volume and LV mass differ significantly in patients with predominantly systolic versus diastolic heart failure.<sup>15</sup> Therefore, an approach integrating LV functional and structural indices is needed for a more complete and useful phenotypic characterization of cardiac performance throughout the adult lifespan.

In the present study we propose a global structural and functional index (LVGFI) that combines the LV SV, end-systolic and end-diastolic volumes as well as LV mass using data from the Multi-Ethnic Study of Atherosclerosis (MESA) obtained during the baseline examination. We evaluate the ability of LVGFI to predict adverse cardiovascular events during 7.2±1.5 (mean±SD) years of MESA follow up and, as secondary endpoints, we compare the relationship of LVGFI to cardiovascular events relative to those of LVMVR, LVEF and the LV mass index during the follow up period.

## Methods

### Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter prospective cohort study of healthy individuals. Details of its methodology have been previously published.<sup>16</sup>

### Cardiac MRI

The complete MRI protocol as well as details on image analysis, data quality control, calculations for LVEF, LV mass and volumes and reproducibility of these global LV measurements have been published previously.<sup>17</sup> LV mass was indexed to body size by dividing the raw LV mass by height raised to the power of 2.7.<sup>18</sup>

### Left Ventricular Global Function Index

The LV global function index (LVGFI) was defined for each participant according to the following formula:

$$\text{LVGFI} = (\text{LVSV} / \text{LV global volume}) * 100$$
, where LV global volume was defined as the sum of the LV mean cavity volume  $[(\text{LVEDV} + \text{LVESV}) / 2]$  and the myocardium volume.

As LV mass is calculated as the product of LV myocardial volume and myocardial density (1.05 g/mL) myocardial volume was extracted prior to the calculation of mass. Thus, the corresponding LVGFI value was expressed as a percentage. Inter- and intraobserver reproducibility levels for LV mass, LVEDV, LVESV, stroke volume and LVGFI are reported on the online supplement material. The theoretical variation of LVGFI and LVEF in various pathophysiological settings are compared in Figure 1.

A healthy MESA reference population was defined without obesity, hypertension (or hypertension medication use), diabetes (or diabetes medication use), smoking habitus or hypercholesterolemia [high-density lipoprotein (HDL) cholesterol < 40 mg/dL, or lipid lowering medication use] of study participants (n=857; age 58±10 years; female 60.6%; African American 14.0%, Caucasian 40.5%, Chinese 25.0%, Hispanic 20.5%). The distribution of the LVGFI was assessed in the reference group and the thresholds for quartile distribution in the total MESA population were then set a priori on the values obtained within this reference population.

### Cardiovascular Events during the Follow-up Period

The primary outcome measure for this study was incident symptomatic heart failure (HF) as defined in prior reports.<sup>9</sup> We also assessed two secondary outcome measures defined a priori in MESA based on pre-specified clinical event definitions: 1) hard cardiovascular events including hard coronary events (myocardial infarction, resuscitated cardiac arrest and death from coronary disease) plus fatal and nonfatal stroke; 2) combined endpoint including all previous event categories in addition to all cause mortality, angina and coronary revascularization (percutaneous coronary intervention or coronary artery bypass surgery). In this final category, only the first clinical event was reported for each participant. A precise definition of each individual outcome and adjudication of clinical event for the MESA study are available online (<http://www.mesa-nhlbi.org/>).

### Statistical Analysis

Detailed description of statistical analyses is reported in the on-line supplemental material for this article. All statistical analyses were performed using STATA (version 11.0, College Station, TX, USA) and two sided p-values <0.05 was considered to be significant.

Briefly, unadjusted univariable Cox Proportional Hazards Models were used to evaluate the effects of each LV variable on the time-to-event probabilities separately for each of the clinical endpoints.

Then, in the multivariable survival analysis, the association between LVGFI or all other LV variables and time-to-event was analyzed adjusting for age, gender, ethnicity, diabetes, systolic blood pressure, diastolic blood pressure, current smoking, body mass index, antihypertensive or lipid lowering therapy, HDL-cholesterol, total plasma cholesterol, Agaston coronary calcium score, Glomerular Filtration Rate, CRP, and NT-proBNP.

## Results

### Clinical Characteristics of the MESA Study Cohort and Cardiovascular Events

Among the 6814 participants of the MESA cohort, 5000 (73%) underwent a baseline cardiac MRI examination. The baseline characteristics of the study population according to the presence or absence of cardiovascular events are presented in Table 1. Over a mean follow-up period of  $7.2 \pm 1.5$  years, heart failure developed in 112 (2.2%) participants and 216 (4.3%) experienced a hard cardiovascular event. Combining all pre-specified clinical events together and reporting only the first event for each patient, 579 (11.6%) participants had a cardiovascular event in this same time period.

### Left Ventricular Global Function Index in a healthy reference group- distribution and relationship to LVEF, LVMVR and indexed LV mass

First, we assessed the relationship between SV and absolute LV mass and LV mean cavity volume respectively (Figure 2). The LVSV was closely related to both LV mean cavity size ( $R^2=0.65$ ;  $P<0.001$ ) as well as absolute LV mass ( $R^2=0.59$ ;  $P<0.001$ ). The distribution of LVGFI was left-skewed with a mean of  $42 \pm 6\%$  and  $40 \pm 7\%$  for the healthy reference group and the entire study population, respectively. The cutoff point for the lower 25<sup>th</sup> percentile in the healthy reference group was of 37%. The specific characteristics of each LV parameter for participants with and without selected cardiovascular events are reported in Table 1.

The relationship with LVGFI and normal values of other functional LV parameters are reported in the on-line supplemental material for this article.

### Relationship of the Left Ventricular Global Function Index to incident HF

The results of unadjusted and adjusted Cox proportional hazard models are shown in Table 2 for each LV parameter and each clinical end-point. Both LVGFI and LVEF were negatively associated with incident HF before and after adjustment for risk factors and biomarkers (after adjustment, LVGFI, HR=0.64 per 1 SD increment,  $p<0.0001$ ; LVEF, HR= 0.68 per 1 SD increment,  $p<0.0001$ ). LV mass index was positively associated with incident HF (HR=1.29 per 1 SD increment;  $p<0.0001$ ). Importantly, LVMVR was not significantly associated with incident HF in the fully adjusted model ( $p=0.8$ ).

When LVGFI was categorized in quartiles, a LVGFI value below 37% was associated with almost a five-fold increase in the incidence of HF in comparison to the upper 75<sup>th</sup> percentile ( $p<0.0001$ ) with a significant difference in the cumulative hazard by log-rank test (Figure 4). The other baseline variables with an independent predictive value on the incidence of HF in the multivariate analysis were heart rate (HR=1.04;  $p=0.02$ ), presence of diabetes (HR=2.58;  $p=0.01$ ) and increased levels of log NT-pro BNP (HR=2.44;  $p<0.0001$ ).

### Relationship of the Left Ventricular Global Function Index to Hard Cardiovascular Events

LVGFI was also negatively associated with incident hard cardiovascular events (nonfatal myocardial infarction, resuscitated cardiac arrest and death from coronary disease plus fatal and nonfatal stroke before, and after adjustment for all other predictors (LVGFI, HR=0.79 per 1 SD increment,  $p=0.007$  in the fully adjusted model). When LVGFI was categorized in quartiles, a LVGFI value below 37% was associated with a strong trend of more than a two-fold increase in the incidence of hard CVD in comparison to the upper 75<sup>th</sup> percentile ( $p=0.07$ ) and there was a significant difference in the cumulative hazard by log-rank test (Figure 4). For hard cardiovascular events the adjusted predictive value of LVEF was not significant, ( $p=0.8$ ). Both LVMVR (HR=1.27;  $p<0.0001$ ) and the LV mass index (HR=1.20  $p=0.008$ ) had positive significant predictive values on incident hard CVD in the fully adjusted model.

### Relationship of the Left Ventricular Global Function index to All Events (Composite Endpoint of hard cardiovascular events, all cause mortality, angina and coronary revascularization)

After adjustment for risk factors and biomarkers, LVGFI was significantly associated with the incident composite endpoint (LVGFI, HR=0.79 per 1 SD increment,  $p<0.0001$ ) and so was the LVEF (HR=0.89;  $p=0.01$ ). A LVGFI value below 37% was significantly associated with a 60% increase in the composite endpoint incidence in comparison to the upper quartile ( $p=0.012$ ) with a significant difference in the cumulative hazard by log-rank test (Figure 4). Moreover, both the LV mass index (HR=1.30;  $p=0.001$ ), and the LVMVR were significantly associated (HR=1.16;  $p=0.001$ ) with the incident composite endpoint.

### Comparison of Models Performance

As reported in Figure 5 the area under the curve (AUC) for the unadjusted predictive value of each LV parameter for each clinical outcome was statistically significant. The AUCs obtained with LVGFI and LV mass index for HF were significantly greater than those obtained with LVEF and LVMVR ( $p<0.0001$ ). Moreover, for hard cardiovascular events and all clinical events combined, the AUCs obtained with LVGFI, LV mass index and LVMVR were significantly greater than those obtained with LVEF ( $p<0.0001$  respectively). As reported in Figure 6, the AUCs for the predictive value of each LV parameter as determined in the fully adjusted on each clinical outcome was not significantly different when the LV parameter remained independently significant in the model. For incident HF, LVMVR was not significantly associated and for incident hard cardiovascular events, LVEF was not significantly associated. This indicates that only LVGFI and indexed LV mass remained independent significant predictors for all clinical outcomes.

Results from the ranking of each model and its corresponding LV parameter with the Akaike Information Criterion are presented in Table 3. For incident HF the best model was obtained with LVEF; for incident hard cardiovascular events the best model fit was obtained with LVMVR and for the composite clinical endpoint, the best model was obtained with LVGFI (Table 3). This suggests that, as LVGFI integrates LV remodeling as well as LV systolic performance information, it is a more comprehensive and reliable predictor of combined CV events.

## Discussion

The current study demonstrates that in a large multi-ethnic cohort without symptoms of cardiovascular disease at enrollment, the LV global function index (LVGFI) that integrates structure and function is independently associated with the subsequent development of heart failure, hard cardiovascular events and a combined endpoint of all adverse events.

Furthermore, a LVGFI below 35% confers between 1.5 to two-fold of risk for incident heart failure, total mortality and combined adverse atherosclerotic events over a mean follow-up of 7.2 years. While LVEF, LVMVR and LV mass index provided risk stratification for different types of incident adverse clinical endpoints similar to the LVGFI when a fully adjusted multivariate model was used, LVGFI remained the most robust predictor in all 3 categories. This suggests that LVGFI is a more reliable LV functional index because it reflects cardiac performance for different degrees of structural LV remodeling.

Our results show that defining a new functional index combining left ventricular global systolic performance information with anatomical LV parameters affected by remodeling is efficient. Although the LVGFI is strongly related to LVEF, it carries additional information that makes it more robust than LVEF, LVMVR and LV mass for predicting different categories of cardiovascular events. With the development of new and more reliable imaging techniques, cardiac remodeling classified as isolated cardiac hypertrophy or as hypertrophy in combination to left ventricular dilation, has received recent attention in the quest for defining better prognostic and therapeutic targets particularly in the setting of pre-clinical cardiovascular diseases.<sup>1, 2</sup> Our results support the hypothesis that LV remodeling and performance is best described by a combination of structural and functional parameters. Another important finding of this study resides in the intrinsic value of each LV parameter to predict different categories of cardiovascular events. As shown in Figure 5, the integration of SV, LV volumes and LV mass in one single multidimensional parameter, improves the stability of the predictive index over different categories of CV events.

The limits of LVEF, the most used LV functional index in clinical routine are clearly shown here, with its lower intrinsic value across all event categories except heart failure. LVEF is a basic global functional marker of systolic function that has become a cornerstone for routine risk stratification and therapeutic strategy decision in patients with cardiovascular disease.<sup>19, 20</sup> However, this parameter has been criticized recently on its lack of sensitivity and specificity to predict subsequent adverse cardiovascular events.<sup>5</sup> This is particularly true at the sub-clinical stages of cardiovascular disease and was clearly shown in the CHARMES study in diastolic heart failure patients, where LVEF was not a significant predictor of death and heart failure hospitalization.<sup>8</sup> One reason might be that significant LVEF changes appear later in the pathological process and are preceded by significant compensatory modifications in LV mass and volumes in order to preserve systolic function. This is true in untreated hypertensive patients where LVEF remains unchanged across a broad range of increasing hypertension categories despite significant increase in LV wall stress and LV wall thickness.<sup>21</sup> LVEF does not account for important predictors of remodeling such as LV mass and this might be one reason why the novel global function index remains significant in all conditions whereas LVEF is not.

The limitations of LVMVR for the prediction of incident heart failure events on the other hand, are also demonstrated. In diastolic HF, LVMVR values are significantly increased, whereas they remain in the normal range for systolic HF.<sup>14</sup> On the contrary, indexed LV mass had the highest intrinsic predictive value for HF events and this can be explained by the significance of LV hypertrophy as an important compensatory mechanism in both systolic (eccentric remodeling) and diastolic (concentric remodeling) HF.<sup>1</sup>

Several studies have demonstrated associations between LV remodeling including indexed LV mass and end-diastolic volumes to cardiovascular events.<sup>9-12, 22</sup> In a recent report from the MESA study, Bluemke et al. showed that LV mass and LV mass-to-volume ratio adjusted to body size with a complex allometric approach were both independently predictive of HF events and stroke.<sup>9</sup> Our hazard ratios and significance level results in the same population confirm the powerful independent predictive value of LV mass with the

limited predictive value of LVMVR on heart failure events. Conversely, LVMVR remained a significant independent predictor of hard CV events (mainly atherosclerotic in nature) possibly by better reflecting the overall cardiovascular fibrosis process but possibly also by lowering the threshold for symptoms in the setting of myocardial ischemia, cerebrovascular occlusion and non-fatal myocardial infarction.

This study also supports the concept that normalized LV mass measured by MRI is a very strong predictor of adverse cardiovascular events,<sup>9, 22, 23</sup> and despite being a weaker predictor of events than the LVGFI for total combined events, it was the only index that remained significant in the presence of LVGFI throughout all endpoint categories in the full multivariate model. The power of LV mass normalized by body size is large part secondary to its place in the causation pathway of multiple CV disease processes including hypertension, diabetes, ischemia, obesity and inflammation.<sup>12, 24-28</sup> This was also shown with LV mass or end-diastolic wall thickness measured by echocardiography. LV mass has a continuous relationship with cardiovascular risk in essential hypertensive patients,<sup>29</sup> and concentric hypertrophy and its persistence despite hypertensive treatment are powerful predictors of cardiovascular outcome in hypertensive patients.<sup>30</sup>

The assessment of LVGFI incorporates elements of LVEF as well as of LV MVR and the LV mass index. Importantly, the assessment of SV with respect to total LV volume is a combined functional and structural quantification of whether a given SV is matched by a proper myocardial mass- and LV cavity size. Thus, it includes information of physiological adaptation as well as pathological remodeling by measures of both cavity size and myocardial mass. Average cavity volume was chosen as a marker of cavity size that reflects the LV operating volume and not one of the extreme values like EDV or ESV, and thus should serve as an improved measure of overall cavity size.

### Limitations

The general applicability of our results may be limited by selection and survivor biases. Because MESA participants had no known cardiovascular disease at baseline, the older individuals undergoing MRI in this cohort represents a healthier sample than the general population at large. Finally, the mechanisms by which cardiovascular events are associated with changes in LV structure and function are not entirely elucidated by these observational data. These markers may provide on the other hand important clues to the pathophysiology of untoward cardiovascular outcomes.

### Perspectives

In an ethnically diverse population free of symptomatic cardiovascular disease at baseline, the LV global function index is strongly associated with adverse cardiovascular events during follow-up while LV ejection fraction is not associated with hard cardiovascular events beyond heart failure. These results suggest that a functional parameter (LVGFI) that integrates structural as well as mechanical behavior may have utility both in the prediction of subsequent cardiovascular events and also in providing insight into the pathophysiology of different cardiovascular outcomes.

### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Novelty and Significance

### What is new?

The combination of left ventricular mass, volumes and stroke volume in one single left ventricular global functional index (LVGFI) integrating all the dimensions of the left ventricle functional anatomy is new.

The LV global function index was strongly and consistently associated with adverse cardiovascular events during follow-up across various categories of cardiovascular events.

If the LV global function index predictive power was comparable to indexed LV mass alone, it was more powerful and consistent than LV mass to volume ratio and LV ejection fraction.

### What is relevant?

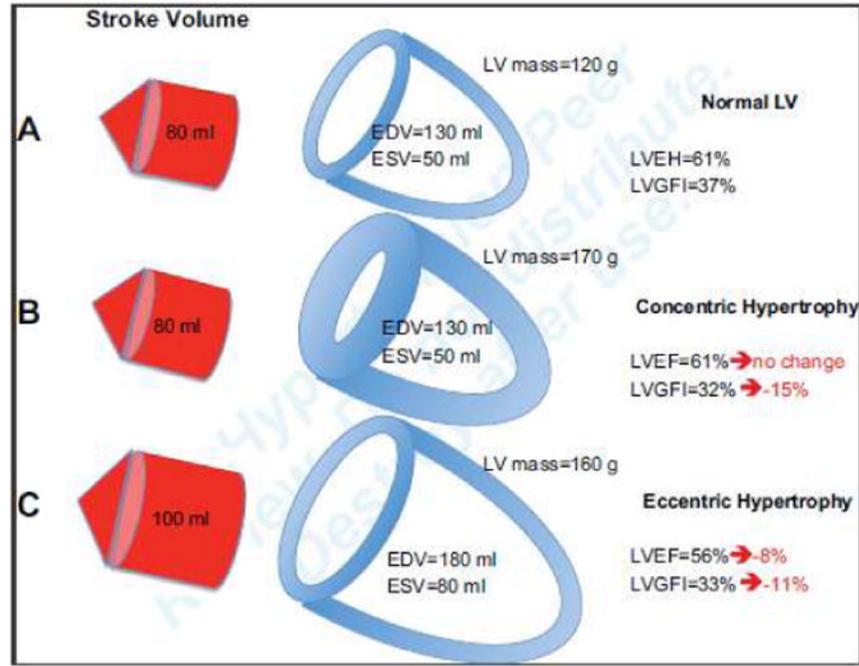
Hypertension impacts left ventricular structure before it alters left ventricular function.

It is essential to have a reliable and reproducible assessment of LV structure and function for the therapeutic management of hypertensive patients.

The LVGFI or indexed LV mass should be integrated on a routine basis in the cardiovascular risk as well as therapeutic management of hypertensive patients.

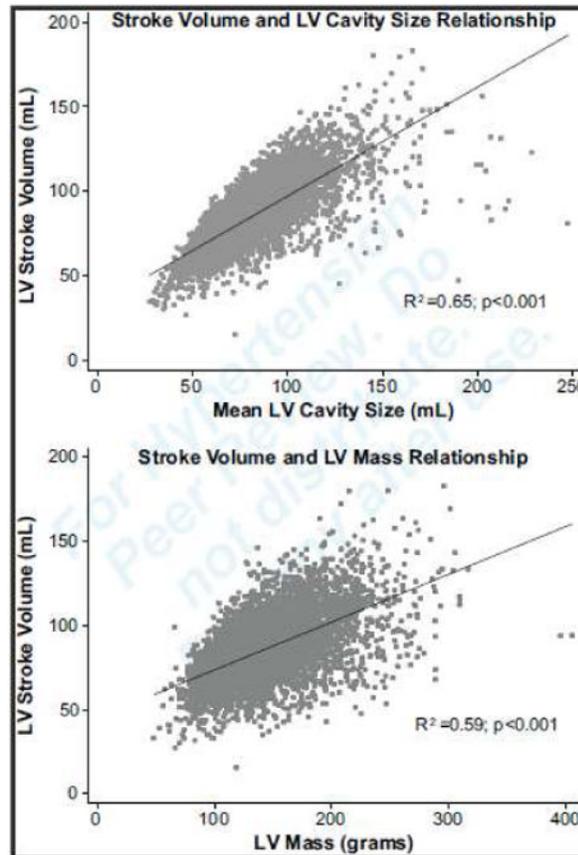
### Summary

In an ethnically diverse population free of symptomatic cardiovascular disease at baseline, the LV global function index is strongly associated with adverse cardiovascular events during follow-up while LV ejection fraction is not associated with hard cardiovascular events beyond heart failure.



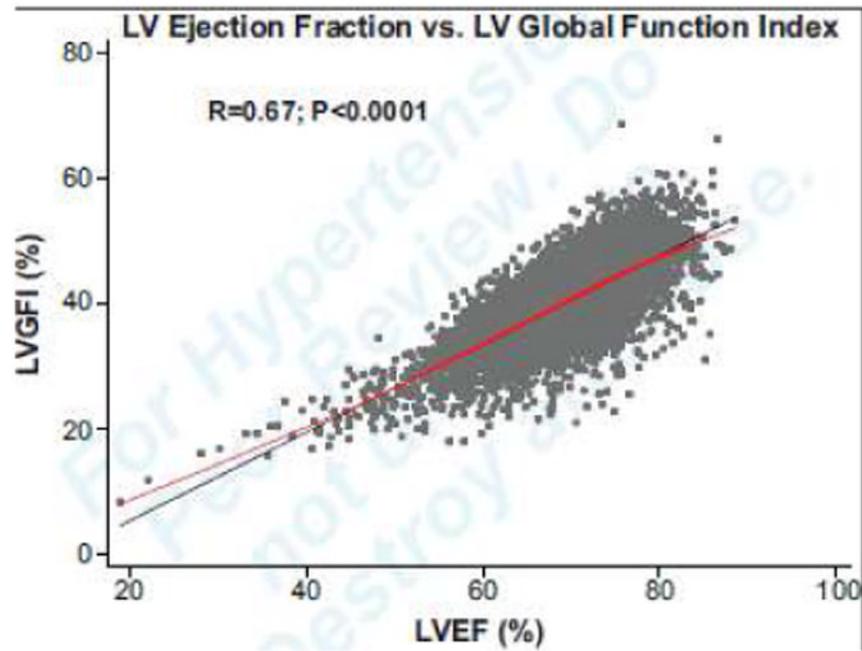
**Figure 1. Schematic comparison of LVEF and LVGFI variations in different sub-clinical pathophysiological settings**

As presented in this figure, LVEF is not sensitive to LV mass variations that are present in concentric hypertrophy (such as in the first stages of hypertensive cardiomyopathy) whereas LVGFI is significantly decreased. In the case of LV eccentric hypertrophy (advanced hypertensive cardiomyopathy, early stages of dilated cardiomyopathy), both functional indices are significantly decreased, but LVGFI is still more decreased than LVEF. Of note:  $LVGFI = [SV / (LVEDV + LVESV / 2 + LVmass / 1.05)] \times 100$ . Concentric hypertrophy is defined by increased LV mass and increased relative wall thickness (RWT). Eccentric hypertrophy is defined by increased LV mass with normal RWT. RWT is calculated as two times the posterior wall thickness divided by the LV end-diastolic diameter and is increased when this ratio is  $> 0.42$ . Increased LV mass is defined as an LV mass  $> 115 \text{ g/m}^2$  in men and  $> 95 \text{ g/m}^2$  in women.

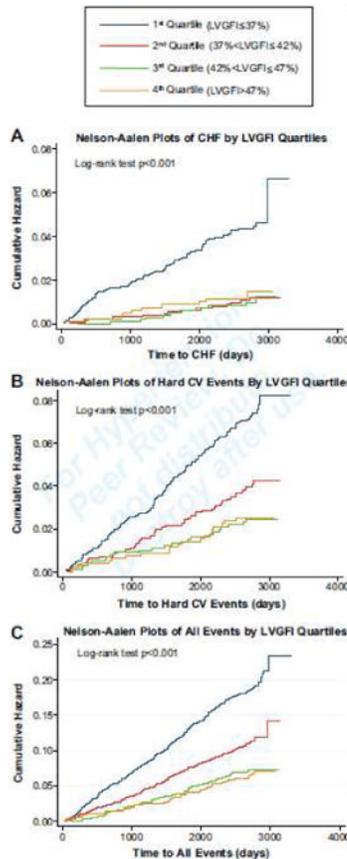


**Figure 2. Relationship between the Left Ventricular Stroke Volume, Mean LV Cavity Size and absolute LV Mass in the whole MESA population**

As discussed in the introduction, SV can be predicted from LV mean cavity size as well as LV absolute mass. LV= left ventricle.

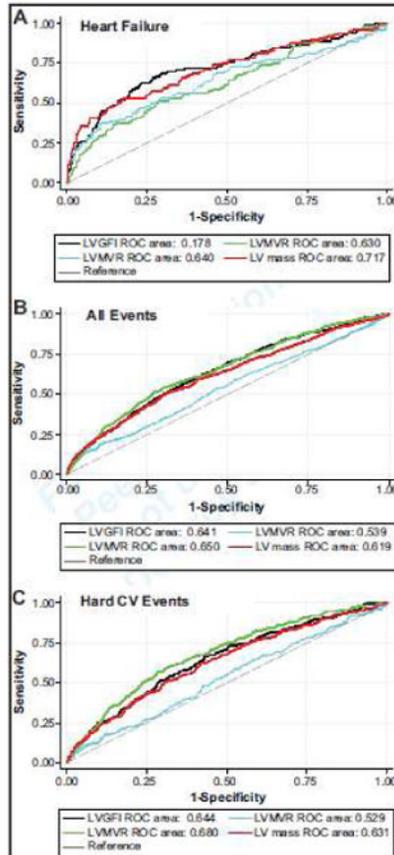


**Figure 3. Correlation plots between LVEF and LVGFI in the whole MESA population**  
Linear (black) and non-linear (red) regression lines are shown. LVGFI=left ventricular global functional index; LVEF=left ventricular ejection fraction.



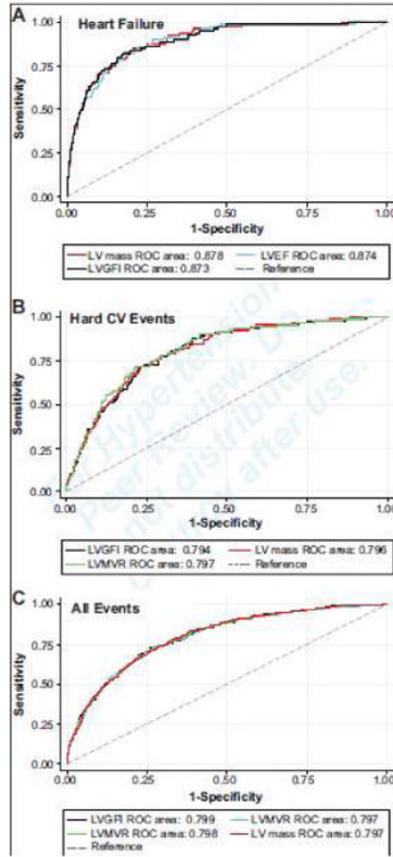
**Figure 4. Nelson-Aalen Analyses for the Different Categories of Clinical Endpoints**

Nelson-Aalen plots illustrating cumulative hazard by quartile of left ventricular functional index (LVGFI) at baseline for (A) heart failure events, (B) hard cardiovascular events, (C) all clinical events. The cumulative hazard was systematically significantly greater in the 1<sup>st</sup> quartile compared to the other quartiles for each end-point (log-rank for difference,  $p < 0.001$ ). The quartile limits were determined in a subset of healthy MESA participants without any cardiovascular risk factors and then applied to the entire MESA population (1<sup>st</sup> quartile < 37 %; 2<sup>nd</sup> quartile from 37 to 42%; 3<sup>rd</sup> quartile from 42 to 47% and 4<sup>th</sup> quartile > 47%).



**Figure 5. Receiver Operating Characteristic (ROC) curves of the predictive power of LVGFI, LVEF, LVMVR and LV mass index determined with a non-adjusted Cox-regression model on the presence/absence of the different clinical outcome categories**

There were significant differences between the different areas under the curve (AUC) obtained with each LV parameter. The AUCs obtained with LVGFI and LV mass index on heart failure were significantly greater than those obtained with LVEF and LVMVR ( $p < 0.0001$ ). For hard cardiovascular events and combined all clinical events, the AUCs obtained with LVGFI, LVMVR and LV mass index were significantly greater than those obtained with LVEF ( $p < 0.0001$  respectively). LVGFI=left ventricular global functional index; LVEF=left ventricular ejection fraction; normalized LV mass=LV mass normalized by body surface area; LVMVR=left ventricular mass to end-diastolic volume ratio; CV=cardiovascular.



**Figure 6. Receiver Operating Characteristic (ROC) curves of the predictive power of LVGFI, LVEF, LVMVR and LV mass index determined with a multivariate Cox-regression model on the presence/absence of the different clinical outcome categories**

There were no significant differences between the different areas under the curve (AUC) obtained with each LV parameter (p=NS). The ROC curves were not computed if the predictive value of the LV parameter didn't reach significance level <0.05 in the full multivariable regression model. LVGFI=left ventricular global functional index; LVEF=left ventricular ejection fraction; normalized LV mass=LV mass normalized by body surface area; LVMVR=left ventricular mass to end-diastolic volume ratio.

**Table 1**  
**Baseline Characteristics of the MESA Study Cohort for Participants With and Without Selected Clinical Events**

Characteristic	No events (n=4,425)	HF (n=112)	Hard CVD (n=216)	All Events (n=579)
Age, yrs	61±10	68±8	67±9	68±9
Male, n (%)	2,015 (46)	75 (67)	133 (62)	367 (64)
Ethnicity, n (%)				
Caucasian	1,712(39)	48 (43)	98 (45)	245 (42)
African American	1,111(25)	35 (31)	53 (25)	174 (30)
Chinese	604(14)	5 (4)	14 (6)	49 (9)
Hispanic	998(22)	24 (22)	51 (24)	111 (19)
Hypertension, n (%)	1,748 (40)	82 (73)	143 (66)	372 (64)
Systolic blood pressure, mmHg	124±21	138±21	138±24	135±23
Diastolic blood, pressure mmHg	72±10	73±11	75±12	74±11
Body mass index, kg/m <sup>2</sup>	28±5	29±5	28±5	28±5
Diabetes, n (%)	478 (11)	34 (30)	50 (23)	116 (20)
Smoking status, n (%)	2,081 (47)	72 (64)	115 (53)	354 (61)
Total cholesterol, mg/dl	195±35	190±35	195±35	191±35
HDL cholesterol, mg/dl	52±15	49±14	48±14	49±15
Hypertension medication, n(%) <sup>*</sup>	1,467 (33)	67 (60)	108 (50)	299 (52)
Lipid lowering medication, n(%) <sup>*</sup>	676 (15)	27 (24)	45 (21)	120 (21)
<b>Left Ventricular Characteristics</b>				
LVEF, %	69±7	64±12	68±8	68±9
LV mass index, g/m <sup>2</sup>	77±15	97±27	86±	85±20
LV mass/ LV volume, g/ml	1.15±0.24	1.30±0.3	1.31±0.27	1.28±0.28
LVGFI, %	40±7	34±9	36±7	37±7

All data are presented as mean ± SD, n(%).CVD= hard cardiovascular disease events, HF= heart failure, HDL= high-density lipoprotein, LV=left ventricle, LVEF= LV ejection fraction, LV mass/ LV volume= LV mass to end-diastolic volume ratio, LVGFI= LV global function index.

<sup>\*</sup> Values are presented for participants taking the medications.

**Table 2**  
**Unadjusted and Adjusted Hazard Ratios of Adverse Clinical Outcome According by the Left Ventricular Global Function Index, Ejection Fraction, Mass to Volume Ratio and Indexed Left Ventricular Mass\***

Models	Unadjusted		Adjusted	
	HR (95%CI)	P-value	HR (95%CI)	P-value
<b>Heart Failure</b>				
LVGFI, % (per 1 SD)	0.44(0.37-0.53)	<0.0001	0.64(0.51-0.80)	<0.0001
LVEF, % (per 1SD)	0.56(0.49-0.64)	<0.0001	0.68(0.57-0.80)	<0.0001
LVMVR, g/ml (per 1SD)	1.51(1.32-1.72)	<0.0001	1.02(0.84-1.25)	0.8
LV mass index (per 1 SD)	1.45(1.32-1.59)	<0.0001	1.29(1.11-1.37)	0.008
<b>Hard Cardiovascular Events</b>				
LVGFI, % (per 1 SD)	0.60(0.53-0.68)	<0.0001	0.79(0.67-0.94)	0.007
LVEF, % (per 1SD)	0.88(0.77-0.99)	0.04	0.99(0.85-1.15)	0.8
LVMVR, g/ml (per 1SD)	1.56(1.42-1.71)	<0.0001	1.27(1.11-1.44)	<0.0001
LV mass index (per 1 SD)	1.45(1.32-1.59)	<0.0001	1.20(1.05-1.37)	0.008
<b>All Events</b>				
LVGFI, % (per 1 SD)	0.60(0.55-0.65)	<0.0001	0.79(0.71-0.88)	<0.0001
LVEF, % (per 1SD)	0.81(0.74-0.88)	<0.0001	0.89(0.81-0.98)	0.01
LVMVR, g/ml (per 1SD)	1.49(1.40-1.58)	<0.0001	1.16(1.06-1.27)	0.001
LV mass index (per 1 SD)	1.76(1.61-1.91)	<0.0001	1.30(1.10-1.51)	0.001

\* All LV parameters values were normalized according to the following formula: (LV parameter-mean value in healthy reference group)/ standard deviation in healthy reference group.

Abbreviations: HR=hazard ratio; CI=confidence interval; LV=left ventricle; LVGFI= LV global functional index; LVEF=LV ejection fraction; LV MVR= LV mass to end-diastolic volume ratio; LV mass index= LV mass indexes to height<sup>2.7</sup>.

**Adjusted Model** includes age, gender and ethnicity, presence of diabetes, systolic blood pressure, diastolic blood pressure, current and former smoking, HDL-cholesterol, total cholesterol, logarithm mean Agatston calcium score phantom-adjusted, Body Mass Index (BMI) and current medications (any anti-hypertensive and/or lipid lowering medication), calibrated glomerular filtration rate, logarithm of N-terminal Pro-B natriuretic peptide (NT-proBNP) and logarithm of C-reactive protein (CRP). BMI was not included in the model with indexed LV mass.

**Table 3**

Akaike Information Criterion for each Cardiovascular End Point by each Left Ventricular Parameter within the full multivariate model.

LV Functional Parameter	CHF	Hard Cardiovascular Events	All Events
LVGFI (%)	1332	2709	<b>7062</b>
LVEF (%)	<b>1328</b>	--	7076
LV MV ratio (g/ml)	--	<b>2705</b>	7069
LV mass index	1336	2710	7072

Akaike Information Criterion ("lower is better") for each LV parameter was obtained with Model 2 (full model). LVGFI= left ventricular global functional index; LVEF= LV ejection fraction; MV ratio= mass to end-diastolic-volume ratio, CHF= Congestive Heart Failure. LV mass index= LV mass was indexed to height raised to the power of 2.7.