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Prediction of All-Cause Mortality and Heart Failure Admissions From Global Left Ventricular Longitudinal Strain in Patients With Acute Myocardial Infarction and Preserved Left Ventricular Ejection Fraction

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Objectives This study sought to test the hypothesis that semiautomated calculation of left ventricular global longitudinal strain (GLS) can identify high-risk subjects among patients with myocardial infarctions (MIs) with left ventricular ejection fractions (LVEFs) >40%.

Background LVEF is a key determinant in decision making after acute MI, yet it is relatively indiscriminant within the normal range. Novel echocardiographic deformation parameters may be of particular clinical relevance in patients with relatively preserved LVEFs.

Methods Patients with MIs and LVEFs >40% within 48 h of admission for coronary angiography were prospectively included. All patients underwent echocardiography with semiautomated measurement of GLS. The primary composite endpoint (all-cause mortality and hospitalization for heart failure) was analyzed using Cox regression analyses. The secondary endpoints were cardiac death and heart failure hospitalization.

Results A total of 849 patients (mean age 61.9 ± 12.0 years, 73% men) were included, and 57 (6.7%) reached the primary endpoint (median follow-up 30 months). Significant prognostic value was found for GLS (hazard ratio [HR]: 1.20; 95% confidence interval [CI]: 1.10 to 1.32; $p < 0.001$). GLS > −14% was associated with a 3-fold increase in risk for the combined endpoint (HR: 3.21; 95% CI: 1.82 to 5.67; $p < 0.001$). After adjustment for other variables, GLS remained independently related to the combined endpoint (HR: 1.14; 95% CI: 1.04 to 1.26; $p = 0.007$). For the secondary endpoints, GLS > −14% was significantly associated with cardiovascular death (HR: 12.7; 95% CI: 3.0 to 54.6; $p < 0.001$) and heart failure hospitalization (HR: 5.31; 95% CI: 1.50 to 18.82; $p < 0.001$).

Conclusions Assessment of GLS using a semiautomated algorithm provides important prognostic information in patients with LVEFs >40% above and beyond traditional indexes of high-risk MI. (J Am Coll Cardiol 2013;61:2365–73) © 2013 by the American College of Cardiology Foundation

Urgent reperfusion, aggressive antiplatelet therapy, and mechanical revascularization have dramatically improved the prognosis of patients with acute myocardial infarction (MI) (1). Left ventricular (LV) systolic dysfunction in the aftermath of an MI has been the target of a range of landmark trials over the previous 2 decades that collectively have established the framework of modern antiremodeling therapies (2,3). Although no studies have formally examined temporal trends in the prevalence of moderate to severe LV systolic dysfunction after MI, it is conceivable that modern management of MI has increased the proportion of patients who survive with only modest reductions in LV systolic function. Not all patients with normal or only modestly reduced left ventricular ejection fractions (LVEFs) have a favorable prognosis. Thus, a measure of systolic function in the setting of preserved LVEF that identifies high-risk patients could potentially be applied to identify those patients who may benefit from greater clinical

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Abbreviations and Acronyms

CI = confidence interval
eGFR = estimated glomerular filtration rate
GLS = global longitudinal strain
HF = heart failure
HR = hazard ratio
IDI = integrated diagnostic improvement
LAVi = left atrial volume index
LV = left ventricular
LVEF = left ventricular ejection fraction
LVMI = left ventricular mass index
MI = myocardial infarction
MR = mitral regurgitation
NRI = net reclassification index
STEMI = ST-segment elevation myocardial infarction
WMSI = wall motion score index

monitoring and alterations in available therapies and as a selection criterion for future randomized studies testing new therapies.

Echocardiographic strain imaging can provide a quantitative measure of subtle LV dysfunction in the setting of preserved LVEF. The main focus has been on the assessment of global longitudinal strain (GLS), reflecting the function of subendocardial longitudinally oriented myocardial fibers, which are especially sensitive to ischemia and increased wall stress (4). Infarct size has been shown to correlate with GLS (5,6), and several studies have documented a relation between GLS and heart failure (HF) with preserved ejection fraction (7,8). Previous studies have shown, that GLS adds prognostic value in chronic HF (9) and in patients with high-risk MI and ST-segment elevation myocardial infarction (STEMI) (10–12) over the entire spectrum of systolic function. However, to the best of our knowledge, no previous prospective study has focused on the prognostic utility of semiautomated GLS assessment in patients with MIs and normal to only modestly reduced LVEFs.

Therefore, we hypothesized that semiautomated GLS assessment could identify high-risk patients with MIs with normal to modestly reduced LVEFs beyond traditional risk factors.

Methods

Study design and patient population. We conducted a prospective study of patients referred for invasive coronary angiography for either STEMI or non-STEMI at 2 tertiary cardiac centers in the Copenhagen region. All patients provided written informed consent before transthoracic echocardiographic examination. Exclusion criteria were age <18 years, noncardiac disease with a life expectancy <1 year, and inability to provide written informed consent. Furthermore, echocardiograms obtained from patients with atrial fibrillation, paced rhythm, or severe aortic stenosis noted at the time of echocardiographic examination was excluded from the analyses.

On the basis of hospital records obtained on admission, information on diabetes mellitus, hypertension, history of ischemic heart disease, and prior MI was registered. Findings on coronary angiography, including culprit lesion, number of diseased vessels, left main coronary artery involvement, and type of revascularization (percutaneous coronary intervention, coronary artery bypass grafting, or no intervention) were registered. Objective signs of HF at presentation or during hospitalization were scored according to the Killip classification scheme (13). Additional biochemical workup included creatinine, hemoglobin, and peak troponin during the hospital stay. Peak troponin I was measured in 226 patients (27%) and peak troponin T in 622 patients (73%). Estimated glomerular filtration rate (eGFR) was measured from the 4-variable Modification of Diet in Renal Disease formula (14). The study was approved by the Regional Scientific Ethics Committee (reference number H-D-2009-063).

Echocardiography. Echocardiography was performed within 48 h of admission to the tertiary center. Echocardiographic cine loops were obtained by recording 3 consecutive heart cycles. All examinations were performed using a Vivid e9 (GE Vingmed Ultrasound AS, Horten, Norway). Images were obtained at a frame rate of at least 60 frames/s and digitally transferred to a remote workstation for offline analysis (EchoPAC BT 11.1.0, GE Vingmed Ultrasound AS). All analyses were performed by a single experienced operator (M.E.) blinded to follow-up information.

Two-dimensional parasternal images were used to determine LV dimensions and wall thickness. Left atrial volume index (LAVI) was determined from the biplane area-length method, and LVEF was determined using the biplane Simpson model. Left ventricular mass index (LVMI) was calculated from the LV linear dimensions in the parasternal view. Volumetric and dimensional measurements of the left ventricle and left atrium were indexed to body surface area when appropriate. All volumetric analyses were performed in accordance with European Association of Echocardiography and American Society of Echocardiography recommendations (15).

Color Doppler examination of the mitral valve was performed in the apical window, and if more than trivial mitral regurgitation (MR) was present, it was quantified by calculating the effective regurgitant orifice area using the proximal isovelocity surface area method. Effective regurgitant orifice area <0.20 cm^2 was considered mild, 0.20 to 0.40 cm^2 moderate, and >0.40 cm^2 severe MR. Doppler recordings of mitral inflow were performed by placing a 2.5-mm sample volume at the tip of the mitral valve leaflets and recording the pulsed-wave Doppler signal. Peak velocities of early (E) and atrial (A) diastolic filling and mitral valve deceleration time were measured, and the E/A ratio was calculated. Pulsed-wave tissue Doppler imaging recordings were obtained at the lateral and medial mitral annulus using a 2.5-mm sample volume with measurements of myocardial peak early velocity (e′). The mean E/e′ ratio was calculated from the mean of lateral and medial values of e′ (16).

Strain analysis. Two-dimensional speckle tracking was performed using a semiautomatic algorithm (Automated Function Imaging, GE Healthcare, Milwaukee, Wisconsin).

Briefly, manual positioning of 3 points (2 annular and 1 apical) was performed in each of the 3 apical projections, enabling the software to semiautomatically track the myocardium throughout the heart cycle. The region of interest was adjusted to cover the thickness of the myocardium. Aortic valve closure was identified on continuous-wave Doppler recording through the aortic valve. The left ventricle was subsequently divided into 17 segments covering the entire myocardium. Careful inspection of tracking and manual correction, if needed, was performed, and in case of unsatisfactory tracking, the segment was excluded from the analysis. The Automated Function Imaging algorithm allowed GLS to be calculated for each of the 3 apical projections if at least 5 of 6 segments were sufficiently tracked. The algorithm then calculated overall GLS as the mean value of all 3 projections. If GLS could be assessed in only 2 of 3 apical projections, we calculated overall GLS as the mean of these 2 values. If GLS could not be assessed in at least 2 of the apical projections, the patient examination was classified as having image quality insufficient for strain measurements.

Follow-up and endpoint definition. The primary outcome was a composite of death from any cause and hospitalization for HF. Information on all-cause mortality was obtained from the Danish Civil Registration System. Information on HF hospitalization was obtained from a systematic review of all hospital admissions after the index MI. Hospitalization for HF was defined as admission because of dyspnea with objective signs of pulmonary congestion and treatment with intravenous diuretic agents. Verification of HF hospitalization was performed by an independent reviewer blinded to echocardiographic information relating to index MI. Cause of death was ascertained from hospital records and classified as either cardiac or noncardiac. The secondary endpoints were cardiac death, hospitalization for HF, and new MI.

Statistical analysis. All data are reported as mean ± SD or median (interquartile range). Baseline clinical and echocardiographic data were analyzed according to GLS quartiles, with categorical and continuous data tested using Cochran-Armitage trend tests and analysis of variance, respectively. All tests were 2 sided, and statistical significance was defined as $p < 0.05$. Interobserver and intraobserver reproducibility was assessed in 20 randomly selected patients using Bland-Altman analysis.

The optimal predictive cutoff value of GLS was found by maximizing the partial likelihood, and the Kaplan Meier estimate for the combined endpoint was plotted using this cutoff value. Univariate Cox proportional hazard regression analyses was performed to analyze the relationships between covariates with known or suspected relationships with the primary endpoint. Backward elimination was performed on a model consisting of all the covariates from the univariate analyses to obtain a parsimonious model.

The relative importance of GLS in relation to echocardiographic parameters was assessed in a model adjusted for LAVI, E/e′ ratio, moderate to severe MR, LVMI, LVEF, and wall motion score index (WMSI), which have all been associated with outcome after acute MI. To assess the importance of GLS in relation to clinical covariates, we adjusted in a multivariate Cox model for age, diabetes, history of hypertension, Killip class >1, eGFR, troponin, and infarct classification as forced-entry covariates. This was based on previous studies that considered both diabetes and Killip class >1 as valid criteria for classification of high-risk MI despite preserved LVEF (17) and infarct classification to assess the possible influence of STEMI or non-STEMI. Peak troponin was entered as quartiles of either troponin T or troponin I. The multivariate models were assessed for assumptions of linearity and proportionality with cumulated Martingale and Schoenfeld residuals, respectively. No violations of linearity or proportionality were found. Incremental model performance was assessed with −2 log likelihood.

Reclassification analysis with arbitrary risk categories of 0% to 5%, 5% to 10%, and >10% was used to assess integrated diagnostic improvement (IDI) and net reclassification index (NRI) when adding GLS to the conventional measures of LV systolic function (LVEF and WMSI) (18). Furthermore, IDI and NRI were evaluated when adding GLS higher than the cutoff value to a model consisting of Killip class >1, diabetes, LVEF, and WMSI. This was based on the presumption that these covariates carry the most impact in daily clinical decision making and risk stratification in patients with acute MIs and LVEFs >40%.

To evaluate the direct effect of GLS on the secondary outcomes of cardiac death, HF admission, and new MI, we performed separate univariate and multivariate Cox models for each secondary endpoint. Cumulative incidence curves were drawn for both outcomes stratified according to the optimal predictive value of GLS using cause-specific Cox regression technique allowing for the competing risk. For the cumulative incidence curve for cardiac death, the competing risk was death from other causes, and for HF admission, the competing risk was death from all causes. All analyses were performed using R software (R Development Core Team) with the Survival, RiskRegression, and Publish packages.

Results

Baseline characteristics. A total of 1,110 patients with MIs were prospectively included. Fifty-three patients were excluded because of atrial fibrillation (n = 40), ventricular paced rhythm (n = 5), and severe aortic stenosis (n = 8). Of the 1,057 patients remaining, 51 (5%) were excluded because of poor image quality. Finally, 157 patients (16%) had LVEF ≤40%, leaving 849 patients (84%) with LVEFs >40% (mean age 61.9 ± 12.0, 73% men) for analysis. The baseline clinical characteristics of the patients with LVEFs >40% are shown according to quartiles of GLS in Table 1. The mean value of GLS in patients with LVEFs >40% was −14.5 ± 3.1%. Impaired GLS was associated with

Table 1 Baseline Clinical Characteristics in Patients With LVEFs >40% According to Quartiles of GLS

Characteristic	GLS (%) <−16.7 (n = 212)	−16.7 to −14.6 (n = 212)	−14.6 to −12.1 (n = 213)	>−12.1 (n = 212)	p Value
Age (yrs)	60.2 ± 11.5	61.5 ± 11.5	61.4 ± 12.8	64.7 ± 12.0	<0.001
Men	140 (66.0%)	157 (74.1%)	166 (78.3%)	153 (72.2%)	0.083
BMI (kg/m^2)	25.9 ± 3.7	26.9 ± 4.4	27.3 ± 4.4	27.2 ± 4.3	0.01
Medical history					
Hypertension	82 (38.7%)	86 (40.6%)	96 (45.3%)	109 (51.4%)	0.002
Previous MI	22 (10.4%)	20 (9.4%)	27 (12.7%)	20 (9.4%)	0.42
Diabetes	19 (9.0%)	24 (11.3%)	23 (10.8%)	34 (16.0%)	0.04
Smoking	151 (71.2%)	146 (68.9%)	154 (72.6%)	137 (64.6%)	0.13
Heart failure	6 (2.8%)	5 (2.4%)	6 (2.8%)	11 (5.2%)	0.08
eGFR (ml/min/1.73 m^2)	83.2 ± 9.9	80.0 ± 11.8	80.5 ± 14.6	77.4 ± 16.4	<0.001
Troponin T (ng/ml)	1.6 ± 2.1	3.0 ± 3.5	3.4 ± 4.0	5.7 ± 4.9	<0.001
Killip class >1	4 (1.9%)	15 (7.1%)	20 (9.4%)	47 (22.2%)	<0.001
Heart rate (beats/min)	66.6 ± 10.3	69 ± 11.4	71.3 ± 11.9	77.1 ± 12.7	<0.001
Blood pressure (mm Hg)					
Systolic	131 ± 19	134 ± 22	131 ± 20	126 ± 20	<0.001
Diastolic	79 ± 11	80 ± 13	80 ± 11	80 ± 12	0.19
Infarct classification					
Non-STEMI	92 (43.4%)	66 (31.1%)	66 (31.1%)	48 (22.6%)	<0.001
STEMI	120 (56.6%)	146 (68.9%)	146 (68.9%)	164 (77.4%)	<0.001
LAD involvement	42 (19.9%)	58 (27.4%)	78 (36.8%)	136 (63.7%)	<0.001
Multivessel disease	23 (10.8%)	20 (9.4%)	32 (15.1%)	37 (17.5%)	0.01
Intervention					0.03
Primary PCI	113 (53.3%)	133 (62.7%)	133 (62.7%)	147 (69.3%)	
Subacute PCI	40 (18.9%)	40 (18.9%)	34 (16.1%)	32 (15.1%)	
No PCI	59 (27.8%)	39 (18.4%)	45 (21.2%)	33 (15.6%)	
Additional CABG	14 (6.6%)	13 (6.1%)	19 (9.0%)	17 (8.0%)	0.20

Values are mean ± SD or n (%).

BMI = body mass index; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; GLS = global longitudinal strain; LAD = left anterior descending coronary artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

increasing age, hypertension, diabetes, in-hospital HF assessed by Killip class >1, proportion of STEMI, left anterior descending coronary artery involvement, and multivessel disease.

The relationships between echocardiographic parameters and quartiles of GLS are shown in Table 2. Progressively impaired GLS was significantly associated with increased LV dilation, increased LVMI, reduced LVEF, and higher

Table 2 Baseline Echocardiographic Characteristics According to Quartiles of GLS

Characteristic	GLS (%) <−16.7 (n = 212)	−16.7 to −14.6 (n = 212)	−14.6 to −12.1 (n = 213)	>−12.1 (n = 212)	p Value
LVEDV (ml)	81 ± 24	82 ± 22	86 ± 24	87 ± 27	0.046
LVESV (ml)	34 ± 13	37 ± 13	41 ± 15	45 ± 17	<0.001
LVEF (%)	58 ± 7	55 ± 7	52 ± 7	49 ± 7	<0.001
WMSI	1.2 ± 0.2	1.3 ± 0.2	1.4 ± 0.2	1.6 ± 0.2	<0.001
LVMi (g/m^2)	84 ± 19	87 ± 20	88 ± 23	96 ± 28	<0.001
LAVi (ml/m^2)	35 ± 12	34 ± 9	33 ± 11	34 ± 10	0.39
E/e′ ratio	9.1 ± 3.0	9.8 ± 3.3	10.2 ± 3.9	11.9 ± 4.8	<0.001
E/A ratio	1.1 ± 0.4	1.0 ± 0.3	1.0 ± 0.4	1.0 ± 0.5	0.37
MV DT (ms)	199.9 ± 46.0	199.3 ± 50.4	193.9 ± 48.0	177.3 ± 52.5	<0.001
Moderate to severe MR	3 (1.4%)	3 (1.4%)	6 (2.8%)	8 (3.8%)	0.38
TR PG (mm Hg)	20.3 ± 10.2	19.8 ± 10.5	18.5 ± 9.4	20.7 ± 11.1	0.19
TAPSE (cm)	2.4 ± 0.4	2.3 ± 0.4	2.1 ± 0.4	2.0 ± 0.4	<0.001

Values are mean ± SD or n (%).

DT = deceleration time; LAVi = left atrial end-diastolic volume index; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVMi = left ventricular mass index; MR = mitral regurgitation; MV = mitral valve; PG = peak gradient; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; WMSI = wall motion score index; other abbreviations as in Table 1.

WMSI. Elevated E/e′ ratio was consistently associated with impaired GLS, but LAVI was not significantly associated with impaired GLS.

Prognostic value of GLS. During follow-up (median 30.0 months; interquartile range: 24.3 to 32.8 months), 57 patients (6.7%) reached the composite endpoint (42 patients [5.0%] died and 15 patients [2.0%] were hospitalized for HF), and no patients were lost to follow-up. A cutoff value of GLS >−14% (hazard ratio [HR]: 3.21; 95% confidence interval [CI]: 1.82 to 5.67; $p < 0.001$) maximized the partial likelihood and identified 373 patients, of whom a cumulative 7.5% and 10% experienced the combined endpoint by 12 and 24 months, respectively. In contrast, a cumulative 2% and 3% of patients with GLS <−14% (n = 475) experienced the combined endpoint at 12 and 24 months, respectively. The Kaplan-Meier estimate dichotomized according to GLS >−14% is reported in Figure 1 (log-rank chi-square = 18.1, $p < 0.0001$). In univariate analyses, GLS provided the second highest C-statistic, surpassed only by age, and after backward elimination, GLS remained significant along with age, eGFR, and a restrictive filling pattern (mitral valve deceleration time <140 ms) (Table 3).

GLS continued to be an independent predictor of the composite endpoint when adjusted for LAVI, E/e′ ratio, moderate to severe MR, LVEF, LVMI, and WMSI (Table 4), but the E/e′ ratio was the only covariate that maintained an independent prognostic value ($p = 0.01$), while LAVI was only borderline significant ($p = 0.06$). When adjusted for age, diabetes, history of hypertension, Killip class >1, troponin, eGFR, and infarct classification, GLS continued to have independent prognostic value (HR: 1.14; 95% CI: 1.04 to 1.26; $p = 0.007$), and only age (HR: 1.05; 95% CI: 1.03 to 1.08; $p < 0.001$) and eGFR (per 10 ml/m^2 decrease, HR: 1.17; 95% CI: 1.01 to 1.36) maintained significant prognostic value along with GLS (Table 4). Addition of GLS to the clinical covariates significantly increased the −2 log likelihood ($p = 0.006$).

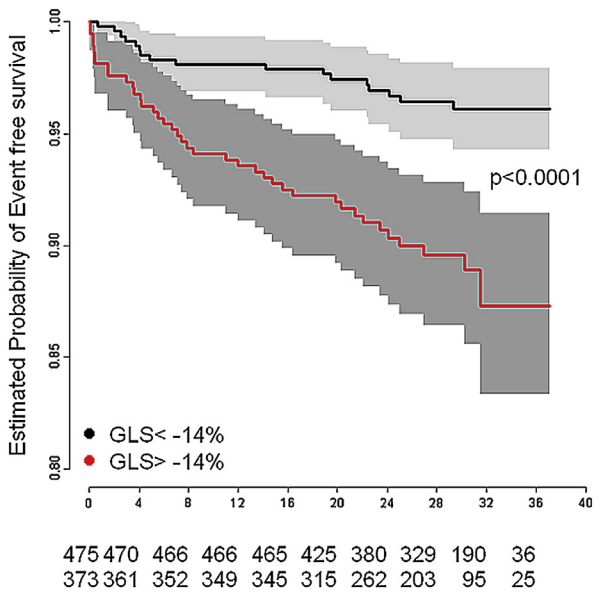

Figure 1 **Kaplan-Meier Curve Showing Freedom From the Combined Endpoint in 848 Patients With LVEFs >40% After Myocardial Infarction**

Patients with global longitudinal strain (GLS) > −14% (n = 373) had increased risk for the combined endpoint of all-cause mortality and heart failure admission ($p < 0.001$). Time indicates months after echocardiography in relation to the myocardial infarction.

Added value of GLS in relation to predicting outcome. Reclassification analysis of adding GLS to LVEF and WMSI yielded a significant IDI (0.89%, $p = 0.012$) and NRI (0.20, $p = 0.014$), driven both by correct net upward risk reclassification in patients with events ($NRI_{event} = 0.16$, $p = 0.040$) and correct net downward reclassification in those without events ($NRI_{nonevent} = -0.05$, $p = 0.032$) (Table 5). When adding GLS >−14% to a model consisting of Killip class >1, diabetes, LVEF, and WMSI, a significant increase in IDI occurred (0.82%, $p = 0.009$), whereas NRI was only borderline statistically significant (0.11, $p = 0.09$).

GLS in relation to cause-specific outcomes. A total of 21 patients (2.5%) died of cardiac causes, and noncardiac death occurred in 22 patients (2.6%). In univariate analysis, GLS was significantly associated with both cardiac death (HR: 1.37; 95% CI: 1.17 to 1.61; $p < 0.001$) and HF hospitalization (HR: 1.52; 95% CI: 1.23 to 1.87; $p < 0.001$), and GLS >−14% was associated with 12-fold and 5-fold increases in risk for cardiac death (HR: 12.7; 95% CI: 2.95 to 54.57; $p < 0.001$) (Fig. 2) and HF admission (HR: 5.31; 95% CI: 1.50 to 18.82; $p < 0.001$) (Fig. 3), respectively, whereas GLS >−14% was not associated with noncardiac death (Fig. 2). After multivariate adjustment with clinical covariates, GLS remained an independent predictor of both cardiac death and HF admission (Table 5). There was no prognostic value of GLS, LVEF, diabetes, Killip class >1, or infarct classification for noncardiovascular death ($p > 0.10$ for all), but as expected, both age and eGFR were prognostic. A total of 44 patients (5.2%) had new MIs, and neither GLS (HR: 1.07; 95% CI: 0.98 to 1.15; $p = 0.19$) nor LVEF (HR: 0.96; 95% CI: 0.93 to 1.01; $p = 0.07$) contained prognostic information in relation to the risk for reinfarction, but as expected, diabetes was highly prognostic (HR: 4.64; 95% CI: 2.51 to 8.59; $p < 0.001$).

Finally, Bland-Altman analysis demonstrated a good intraobserver and interobserver agreement, with a small nonsignificant bias for GLS. The mean difference ± 2 SDs for GLS was −0.7 ± 2.5% and −0.5 ± 1.3% for interobserver and intraobserver agreement, respectively.

Discussion

In the largest prospective study to date of patients with MIs undergoing comprehensive echocardiography with deformation imaging, we demonstrate the following: 1) GLS

Table 3 Univariate and Multivariate Results of Combined Clinical and Echocardiographic Cox Regression Models

Variable	HR	95% CI	p Value	C-Statistic	HR	95% CI	p Value
Age, yrs	1.07	1.05–1.10	<0.001	0.72	1.06	1.03–1.08	<0.001
Diabetes	2.00	1.06–3.78	0.033	0.54			
Hypertension	1.66	0.99–2.81	0.057	0.56			
Killip class >1	3.43	1.90–6.20	<0.001	0.58			
Infarct classification	0.87	0.51–1.50	0.628	0.51			
eGFR per 10 ml/m^2 decrease	1.37	1.20–1.57	<0.001	0.64	1.17	1.01–1.36	0.036
Troponin	1.07	1.01–1.14	0.039	0.52			
LVEF	0.96	0.92–0.99	0.014	0.60			
WMSI	4.82	1.80–12.93	0.002	0.62			
E/e′ ratio	1.10	1.06–1.15	<0.001	0.60			
LAVi	1.03	1.01–1.05	0.007	0.61			
MV DT <140 ms	1.96	1.05–3.63	0.034	0.55	1.94	1.02–3.72	0.044
LVMi	1.01	1.00–1.02	0.189	0.58			
Moderate to severe MR	2.52	0.79–8.10	0.119	0.52			
GLS	1.20	1.10–1.32	<0.001	0.65	1.12	1.02–1.22	0.016

CI = confidence interval; HR = hazard ratio. Other abbreviations as in Tables 1 and 2.

calculated using a semiautomatic algorithm available as a bedside tool without the need for time-consuming post-processing enables rapid risk assessment and predicts adverse outcome in patients with LVEFs >40%; and 2) GLS provides independent information related to death or HF admissions in patients with LVEFs >40% over and above well-established risk factors that carry treatment recommendations in current guidelines. Randomized studies should clarify whether patients with MIs, LVEFs >40%, and impaired GLS benefit from antiremodeling therapy.

GLS in relation to myocardial function and prognosis after MI. The prognostic value of GLS may in part be determined by the ability of GLS to reflect infarct size after MI, which has been demonstrated in several studies (5,6). Subendocardial longitudinal fibers are sensitive to hypoperfusion in the setting of ischemia, so GLS may also reflect the area at risk. However, impaired GLS may be seen even in the absence of significant acute myocardial injury, when preexisting conditions adversely affect longitudinal fiber function, such as fibrosis and triglyceride depositions (19,20). Furthermore, the geometric alignment of the endocardial longitudinal fibers results in a smaller curvature and thus exposes them to greater detrimental effect of increased LV cavity pressure because of the law of Laplace (4).

Estimation of LVEF, whether performed by Simpson's method or qualitative scoring of myocardial segments, is a cornerstone in decision making after MI. Currently, antiremodeling treatment after acute MI with angiotensin-converting enzyme inhibitors is indicated in all patients with LVEFs <40% to 45%. Patients with diabetes or in-hospital HF represent a high-risk group even in the setting of an LVEF >40% and as such should also receive angiotensin-converting enzyme inhibitors (17). Aldosterone antagonist treatment is indicated for patients with LVEFs <40% accompanied by in-hospital HF or diabetes (3). Thus, any novel measure of LV systolic dysfunction after acute MI should preferentially be applied in a population with LVEFs >40%, for whom treatment guidelines are less clear. The present study demonstrates that impaired GLS identifies high-risk patients in the setting of LVEF >40% independently and incremental to Killip class >1, diabetes, LVEF, and WMSI, which are among the most important decision-making indexes in patients with acute MIs and LVEFs >40%. Reclassification analysis of GLS with arbitrary risk categories yielded significant improvement over LVEF and WMSI, underscoring the powerful insight into LV dysfunction provided by deformation analysis.

GLS in patients with LVEFs >40%. In the present study, patients with preserved or only modestly reduced LVEFs constituted nearly 85% of our overall population with acute MIs available for analysis and carried a low absolute risk for

Table 4 Relation Between GLS and Outcome

	GLS			
Outcome	Number of Events/ Number of Patients	Unadjusted HR (95% CI)	Adjusted for Echocardiographic Covariates, HR (95% CI)*	Multivariate Adjusted HR (95% CI)†
All-cause death or hospitalization for HF	57/849 (6.7%)	1.20 (1.10–1.32), p < 0.001	1.15 (1.03–1.29), p = 0.01	1.14 (1.04–1.26), p = 0.007
Cardiac death	21/849 (2.5%)	1.37 (1.17–1.61), p < 0.001	1.31 (1.07–1.60), p = 0.009	1.26 (1.06–1.50), p = 0.009
Hospitalization for HF	15/849 (1.8%)	1.52 (1.23–1.87), p < 0.001	1.27 (0.99–1.63), p = 0.06	1.47 (1.17–1.86), p < 0.001

*Adjusted for left atrial volume index, E/e′ ratio, left ventricular mass index, moderate-to-severe mitral regurgitation, and wall motion score index. †Adjusted for age, diabetes, history of hypertension, Killip class >1, estimated glomerular filtration rate, troponin, and infarct classification.

HF = heart failure; other abbreviations as in Tables 1 and 3.

Table 5 Reclassification Table With Added Value of GLS in Relation to Outcome

	Model With LVEF, WMSI, and GLS			
Model With LVEF and WMSI	0%–5% Risk	5%–10% Risk	>10% Risk	Total
Patients with endpoint				
0%–5% risk	7	6	0	13
5%–10% risk	4	17	9	30
>10% risk	0	2	12	14
Total	11	25	21	57
Patients without endpoint				
0%–5% risk	204	58	0	262
5%–10% risk	129	234	61	429
>10% risk	2	28	71	101
Total	335	320	137	792

Net reclassification improvement = 0.20 (p = 0.014).
Abbreviations as in Tables 1 and 2.

the combined endpoint of death and HF hospitalization. However, assessment of GLS using a semiautomatic algorithm and a cutoff of −14% enabled the identification of a smaller subgroup with 3 times higher risk for the combined endpoint, 12 times higher risk for cardiac death, and 5 times higher risk for HF hospitalization, and, importantly, the remaining large group had very favorable outcomes.

Several studies have examined the prognostic value of GLS in unselected populations (21), in stable chronic HF (9,22,23), and recently in patients with chronic ischemic cardiomyopathy (24). The prognostic value of GLS was reported by Hung et al. (11) in 603 high-risk patients with

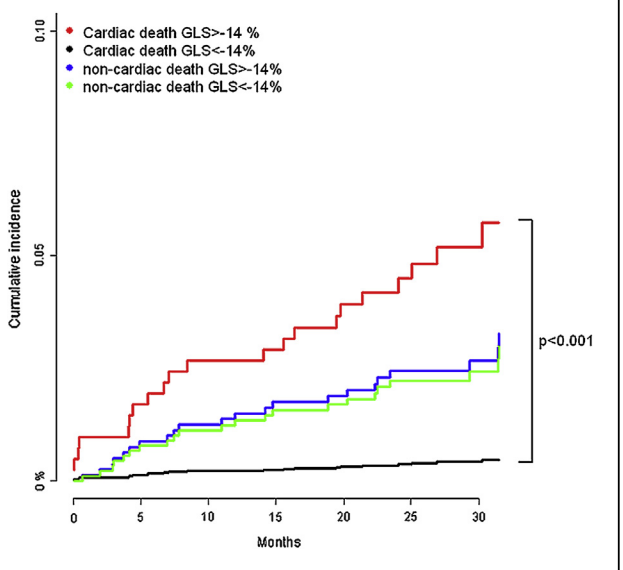

Figure 2 Cumulative Incidence Curve for Cardiac Death With Adjustment for Competing Risk

The red and black curves depict cardiac death stratified according to global longitudinal strain (GLS) >−14% (p < 0.001). The blue and green curves show death from other causes stratified according to GLS >−14%, with no significant prognostic value of GLS.

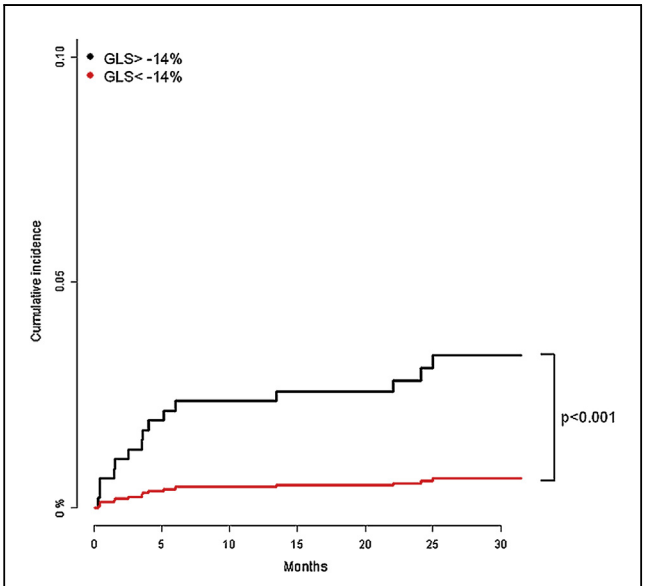

Figure 3 Cumulative Incidence Curve for HF Admission With Adjustment for Competing Risk From Death From All Causes

The red and black curves depict heart failure (HF) admissions stratified according to global longitudinal strain (GLS) >−14% (p < 0.001).

MIs from the Valsartan in Acute Myocardial Infarction study, and both Munk et al. (12) (n = 425) and Antoni et al. (10) (n = 659) demonstrated the prognostic value in STEMI. However, all of these studies were of smaller size, were retrospective in design, and used a time-consuming algorithm for calculating GLS. Furthermore, the studies in STEMI both used reinfarction in the combined endpoint, which was predicted by neither GLS nor LVEF in our study. The study by Munk et al. (12) was pooled from 3 smaller studies and had 75% feasibility for GLS calculation. The combined secondary endpoint in the study by Antoni et al. was driven in large part by elective revascularization, which can often be anticipated from the coronary anatomy obtained at baseline. Furthermore, none of the studies specifically studied a population with preserved or only moderately reduced LVEFs. Finally, the present study is sufficiently large to evaluate the prognostic value of GLS on highly relevant endpoints in a low-risk MI population, for which there are currently no established guidelines for antiremodeling therapies.

Relative importance of GLS compared with diastolic parameters. GLS maintained significant prognostic value when adjusted for E/e′ ratio, WMSI, LVEF, and LAVI, and only E/e′ retained prognostic information. Limited data exist on the combined prognostic value of E/e′ ratio and LAVI in contemporary patients with MIs with LVEFs >40%, but from a physiological point of view, a chronically enlarged left atrium in the absence of MR must imply at least periodically elevated filling pressure (25). The impact of longitudinal myocardial shortening in relation to left atrial

volume has not been explored in detail. Further studies are needed to assess the interaction among left atrial volume, E/e′ ratio, and GLS in contemporarily managed patients with MIs with normal to modestly reduced LVEFs.

GLS in relation to hospitalization for HF and cardiac death. In patients with LVEFs >40%, GLS proved to be predictive of HF hospitalizations, with an unadjusted 5-fold increase in risk according to the optimal cutoff values. This finding is in line with emerging evidence from studies of patients with HF with preserved ejection fraction, in whom distinct systolic abnormalities are apparent despite preserved LVEFs (8). Indeed, in-hospital HF in the acute phase of MI has been shown to be highly associated with GLS (26) and biochemical evidence of neurohormonal activation (27). Although the absolute risk for HF hospitalization in patients with LVEFs >40% was low, the striking independent effect of GLS in this regard warrants further studies of the coupling of reduced long-axis function in the acute phase of MI and subsequent disposition for elevations in filling pressure. The association between GLS and cardiac death remains intriguing, and further studies should be conducted to examine the relationship between deformation patterns in acute MI and disposition for malignant arrhythmias.

Study limitations. Although the present study encompasses the largest population to date with MI and prospective evaluation of GLS in the acute phase, we acknowledge that the feasibility of the semiautomated GLS measurements may have been higher in our case compared with everyday clinical practice. However, recent studies suggest that GLS can be estimated with good reproducibility across different vendor platforms and proprietary software algorithms (28). The multivariate statistical models suffer from overfitting due to the small number of events, which warrant caution for the interpretation, but this strategy can be acceptable when the main focus is on controlling for confounders rather than building prediction models (29). In this study, we did not perform analyses of radial and circumferential deformation, which has previously been shown to contain prognostic information (11), but a number of considerations pertain to this decision: 1) circumferential and radial strain calculations require sufficient short-axis images, ideally at the apical, midpapillary, and mitral levels, which are not always possible to obtain; 2) currently, there is no validated global value for circumferential strain; and 3) currently, no semiautomatic algorithm exists for these calculations. We did not calculate strain rate, because it is not currently available in the semiautomated algorithms. In this study, we enrolled patients with STEMI and those with non-STEMI, but none of the major clinical trials evaluating renin-angiotensin blockade (2,17), aldosterone blockade (3), and device therapy (30,31) in post-MI patients have used the type of infarction as a selection criterion, so no evidence supports a differential importance of systolic dysfunction according to infarct transmurality. None of the echocardiographic exams were performed using contrast, which could potentially have improved image quality and altered the prognostic value of the traditional echocardiographic measurements.

Conclusions

Semiautomated calculation of GLS is significantly related to all-cause mortality or HF admission in patients with MIs and LVEFs >40%, above and beyond traditional identifiers of high risk such as diabetes and clinical HF.

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