Prognostic value of multilayer left ventricular global longitudinal strain in patients with ST-segment elevation myocardial infarction with mildly reduced left ventricular ejection fractions

Abou, R.; Goedemans, L.; Montero Cabezas, J.M.; Prihadi, E.A.; Mahdiui, M. el; Schalij, M.J.; ... ; Delgado, V.

Prognostic Value of Multilayer Left Ventricular Global Longitudinal Strain in Patients with ST-segment Elevation Myocardial Infarction with Mildly Reduced Left Ventricular Ejection Fractions

Rachid Abou, MD, Laurien Goedemans, MD, José M. Montero-Cabezas, MD, Edgard A. Prihadi, MD, Mohammed el Mahdiui, MD, Martin J. Schalij, MD, PhD, Nina Ajmone Marsan, MD, PhD, Jeroen J. Bax, MD, PhD, and Victoria Delgado, MD, PhD*

Multilayer (epi-, mid- and endocardium) left ventricular (LV) global longitudinal strain (GLS) reflects the extent of myocardial damage after ST-segment myocardial infarction (STEMI). However, the prognostic implications of multilayer LV GLS remain unclear. We studied the association between multilayer LV GLS and prognosis in patients with mildly reduced or preserved LV ejection fraction (EF) after STEMI. Patients with first STEMI and LVEF>45% were evaluated retrospectively. Baseline multilayer (endocardial, mid-myocardial and epicardial) LV GLS were measured on 2-dimensional speckle tracking echocardiography. Patients were followed up for of all-cause mortality. A total of 569 patients (77% male, 60 ± 11 years) were included. After a median follow-up of 117 (interquartile range 106-132) months, 95 (17%) patients died. We observed no differences in baseline LVEF and peak troponin levels between survivors and non-survivors. However, non-survivors showed more impaired GLS at all layers (epicardium: -11.9 ± 2.8% vs. -13.4 ± 2.8%; mid-myocardium: -14.2 ± 3.2% vs. -15.6 ± 3.2%; endocardium: -16.5 ± 3.7% vs. -17.7 ± 3.6%, p <0.05, for all). On multivariable analysis, increasing age (hazard ratio 1.095; p<0.001) and impaired LV GLS of the epicardial layer (hazard ratio 1.085; p = 0.047) were independently associated with higher risk of all-cause mortality. In addition, LV GLS at the epicardium had incremental prognostic value for all-cause mortality (χ^2 = 114, p = 0.044). In conclusion, in contemporary STEMI patients with mildly reduced or preserved LVEF, ageing and reduced LV GLS of the epicardium (reflecting transmural scar formation) were independently associated with all-cause mortality after adjusting for clinical and echocardiographic variables. **(Am J Cardiol 2021;152:11−18)**

Non-invasive evaluation of left ventricular (LV) systolic function by two-dimensional (2D) echocardiography remains one of the most important measures in clinical cardiology.[1] Although LV systolic function is conventionally measured by means of the LV ejection fraction (EF), it has become evident that this parameter is subject to a number of limitations.[2] In addition, LVEF can be normal in the presence of impaired LV systolic function, since it does not reflect intrinsic myocardial deformation.[3] LV global longitudinal strain (GLS) measured by speckle tracking echocardiography can overcome these limitations and has shown to be an important prognostic parameter in the risk stratification of patients after acute myocardial infarction.[4] Furthermore, speckle tracking echocardiography allows for comprehensive automated layer-specific analysis (endocardium, mid-myocardial, epicardium; respectively) of the LV myocardial wall. Especially in ischemic heart disease, layer-specific analysis is of interest since the myocardial damage after acute myocardial infarction may not be transmural and the influence on global LV systolic function and prognosis may vary.[5] Layer-specific analysis of LV GLS has shown to accurately discriminate between transmural and non-transmural myocardial infarction and has also been associated with outcome.[6,7] Moreover, all-cause mortality is increased when LVEF<40%, however the prognostic value of low-normal range LVEF remains questionable.[8] Therefore, the aim of this study was to evaluate the prognostic value of multilayer LV GLS in a homogenous patient population with ST-segment elevation myocardial infarction (STEMI) and mildly reduced LVEF (40-49%) or preserved LVEF (≥50%).

Methods

Patients admitted with acute STEMI at the Leiden University Medical Center (The Netherlands) and treated with primary percutaneous coronary intervention were evaluated retrospectively. All patients were treated systematically according to an institutional guideline-based framework (MISSION!).[9] Patients with incomplete follow-up data,

Department of Cardiology, Leiden University Medical Centre, Leiden, The Netherlands . Manuscript received February 20, 2021; revised manuscript received and accepted April 16, 2021.

*Corresponding author. Tel: +31715262020; fax: +31715266809.

E-mail address: V.delgado@lumc.nl (V. Delgado).

https://doi.org/10.1016/j.amjcard.2021.04.033

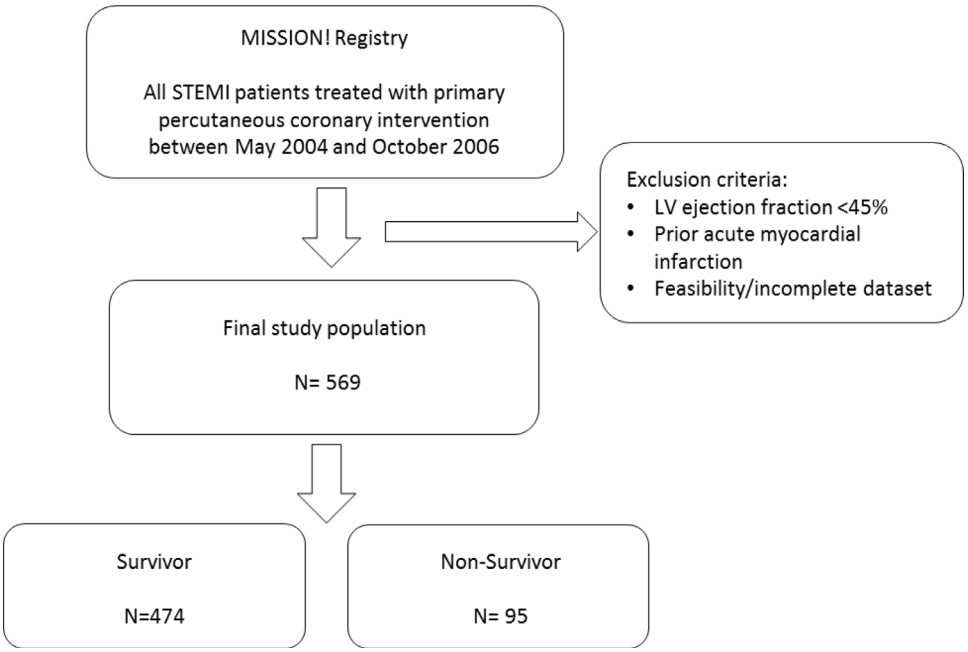

Figure 1. Flowchart of study population. LV = left ventricular; STEMI = ST elevation myocardial infarction.

2D-echocardiographic data not suitable for speckle tracking analysis and known LVEF <45% prior to the index STEMI were excluded from this analysis (Figure 1). Demographic and clinical data were recorded at index admission. For retrospective analysis of clinically acquired data, the Institutional Review Board waived the need of patient written informed consent.

Clinical data were collected in the Cardiology Department Information System (EPD-Vision; Leiden University Medical Center, Leiden, The Netherlands). From the invasive coronary angiography performed upon admission, the culprit lesion was identified and the final Thrombolysis In Myocardial Infarction flow after primary percutaneous coronary intervention was evaluated and registered. Multi-vessel disease was defined as the presence of more than one vessel with luminal narrowing ≥70%. Cardiovascular medications at hospital discharge were recorded and optimized at the discretion of the treating physician.

Within 24-48 hours of admission, 2D-transthoracic echocardiography was performed in patients at rest in the left lateral decubitus position using commercially available ultrasound systems (Vivid 7 and E9; General Electric Vingmed, Horten, Norway). Data acquisition was performed with 3.5-MHz or M5S transducers. Standard M-mode, 2D, color, pulsed and continuous wave Doppler images were acquired and stored digitally for offline analysis (EchoPac BT13; GE Medical Systems, Horten, Norway). LVEF was calculated according current recommendations.[10] The wall motion score index was defined as the total sum of the segmental scores divided by the number of segments scored.[10] LV mass was calculated according the Devereux formula, and indexed for body surface area.[10] Valvular function was assessed with 2D, color, pulsed and continuous wave Doppler echocardiography.[11] Finally, LV diastolic function was assessed with transmitral flow pulsed-wave recordings and the peak early (E) and late (A) diastolic velocities as well as the E-wave deceleration time were measured. The measurement of e´ was performed with tissue Doppler imaging at the septal and lateral mitral annulus in the apical 4-chamber view.[12]

2D-speckle tracking echocardiography was applied to perform a layer-specific analysis (endocardial, mid-myocardial and epicardial) of GLS from the apical 2- and 4-chamber views, as well as the long-axis view of the left ventricle.[13] The software allows for analysis of the global LV longitudinal strain of the 3 different layers: endomyocardial, mid-myocardial and epicardial. As described previously, layer-specific GLS values were obtained as the average of longitudinal strain of 17 LV segments at each individual layer.[14] This analysis was performed off line from clinically stored data. Intra- and inter-observer reproducibility for multi-layer GLS measurements has been previously reported with intraclass correlation coefficients of 0.816 (95% confidence interval; 0.487 to 0.930) and a inter-class correlation coefficients of 0.772 (95% confidence interval; 0.437 to 0.909), respectively.[14]

Survival data were complete for all study subjects and collected from the departmental cardiology information system, which is linked with the municipal civil registries and contains mortality data up to date. Patients were followed for the occurrence of all-cause mortality which is defined as cardiac and non-cardiac mortality.

All statistical analyses were performed with the Software Package for Social Sciences for Windows v23.0 (IBM, Armonk, New York). Categorical data are presented as frequencies and percentages. Continuous data are presented as mean ± standard deviation or median and interquartile range, as appropriate. To compare categorical data between groups, χ2-tests were performed. Continuous data were compared using the unpaired Student t-test or Mann-Whitney U test, as appropriate. Furthermore, Kaplan-Meier analysis was performed for survival rates. The study

population was divided into two groups according to the median of each individual layer. Survival rates were compared with log-rank tests. The association of clinical and echocardiographic variables with all-cause mortality were tested using the Cox proportional hazards analysis. The hazard ratio (HR) and 95% confidence interval (CI) were calculated. Statistically significant predictors in univariable Cox regression analysis ($p < 0.05$) were included in multivariable models. To avoid multicollinearity, a correlation coefficient of >0.7 was set. Finally, to evaluate the incremental value of layer-specific LV GLS over clinical and conventional echocardiographic parameters, layer-specific LV GLS was introduced to a baseline Cox regression model in a stepwise manner. Global $\chi 2$ values were calculated for all individual models. A 2-tailed p-value <0.05 was considered statistically significant.

Results

A total of 569 patients (mean age 60 ± 11 years, 77% male) were included and divided according to survival status at follow-up (Table 1). After a median follow up of 117 (IQR 106-132) months, 95 patients (17%) died. When comparing survivors versus non-survivors, patients who died were significantly older, and more frequently male (, had a higher body mass index and higher heart rates at discharge. There were no differences in frequency of cardiovascular risk factors, infarct size based on peak troponin and peak creatine kinase levels. However, non-survivors showed worse renal function and more often presented with multi-vessel disease and Killip class ≥2. There were no differences in medication use between survivors and non-survivors.

Echocardiographic characteristics for the overall study population, survivors and non-survivors are reported in Table 2. The median LVEF was 57% (IQR 47-57) and the mean wall motion score index was 1.4 ± 0.3. Mean LV GLS was -15.1 ± 3.2% whereas the mean values for LV GLS at epi-, mid- and endocardium were -13.2 ± 2.9%, -15.2 ± 3.2% and -17.5 ± 3.6%, respectively. We observed no difference in baseline LVEF and wall motion score index between survivors and non-survivors. Non-survivors showed significantly smaller LV volumes and more advanced diastolic dysfunction when compared to survivors (Table 2).

The mean LV GLS was more preserved in survivors when compared to non-survivors. In addition, layer-specific LV GLS analysis showed more preserved values for survivors when compared to non-survivors at the endocardium, mid-myocardium and the epicardium.

Table 1
Baseline characteristics for study population

Variable	Total population(n = 569)	Survivor		p-value
		Yes(n = 474)	No(n = 95)	
Age (years)	60 ± 11	58 ± 10	70 ± 11	<0.001
Body mass index (kg/m^2)	26 ± 3.8	26 ± 3.7	26 ± 4.0	0.037
Male gender	437 (77%)	372 (79%)	65 (68%)	0.045
QRS duration, ms	90 (85-100)	90 (86-100)	92 (80-96)	0.262
Systolic blood pressure (mmHg)	137 ± 24	136 ± 23	140 ± 28	0.163
Diastolic blood pressure (mmHg)	81 ± 15	82 ± 15	80 ± 15	0.257
Heart rate discharge, bpm	69 ± 14	68 ± 12	71 ± 14	0.014
Hypertension	179 (32%)	144 (30%)	35 (37%)	0.227
Hypercholesterolemia	110 (19%)	96 (20%)	14 (15%)	0.255
Family history of coronary artery disease	249 (44%)	214 (45%)	35 (37%)	0.142
Diabetes mellitus	48 (8%)	37 (8%)	11 (12%)	0.227
Current smoker	281 (50%)	242 (51%)	39 (41%)	0.091
Peak creatine phosphokinase (U/L)	1266 (622-2418)	1285 (646-2481)	1312 (608-2194)	0.520
Peak cardiac troponin T (μg/L)	3.2 (1.4-6.4)	3.2 (1.4-6.3)	3.5 (1.6-7.2)	0.278
eGFR (ml/min/1.73m^2)	96 ± 31	99 ± 30	81 ± 29	<0.001
Killip class ≥2	19 (3%)	9 (2%)	10 (11%)	<0.001
Culprit vessel left anterior descending coronary artery	353 (62%)	293 (62%)	60 (63%)	0.908
TIMI flow ≥2	562 (99%)	469 (99%)	93 (98%)	0.264
Multi-vessel disease	241 (42%)	191 (41%)	50 (53%)	0.030
Medications at discharge				
Aspirin	547 (96%)	460 (97%)	87 (92%)	0.096
Thienopyridines	564 (99%)	471 (99%)	93 (98%)	1.000
Angiotensin converting enzyme inhibitors/ Angiotensin receptor blockers	550 (97%)	461 (97%)	89 (94%)	0.287
β-blockers	537 (94%)	450 (95%)	87 (92%)	0.437
Statins	561 (99%)	472 (100%)	93 (98%)	0.514

Data are presented as mean ± standard deviation, number (percentage) or as median (25th-75th percentile). bpm = beats per minute; (e)GFR = glomerular filtration rate estimated with the Cockcroft-Gault formula; TIMI = thrombolysis in myocardial infarction. Hypertension was defined as office blood pressure ≥140/90 mmHg or previous pharmacological treatment. Hypercholesterolemia was defined as total cholesterol 190 mg/dl or previous pharmacological treatment. Diabetes mellitus was defined as fasting blood glucose ≥7.0 mmol/L, 2-h oral glucose tolerance test glucose ≥11.1 mmol/L or previous pharmacological treatment. p-values are presented for the comparisons between different groups.

Table 2
Baseline echocardiographic findings for study population

Variable	Total population(n = 569)	Survivor		p-value
		Yes(n = 474)	No(n = 95)	
Body surface area, m^2	2.0 ± 0.2	2.0 ± 0.2	1.9 ± 0.2	<0.001
Left ventricular mass, indexed (g/m^2)	107 ± 28	107 ± 28	109 ± 28	0.534
Left ventricular end-diastolic volume (ml)	98 (77-121)	100 (79-121)	89 (69-112)	0.002
Left ventricular end-systolic volume (ml)	47 (37-57)	48 (37-57)	42 (33-54)	0.033
Left ventricular ejection fraction (%)	52 (47-57)	52 (48-57)	51 (47-56)	0.257
Left ventricular end-diastolic diameter (mm)	47 ± 6	47 ± 5	46 ± 6	0.120
Left ventricular end-systolic diameter (mm)	31 ± 6	31 ± 6	30 ± 7	0.458
Wall motion score index	1.4 ± 0.3	1.4 ± 0.3	1.6 ± 0.3	0.697
Mitral regurgitation ≥2	31 (6%)	22 (5%)	9 (10%)	0.077
E-prime (cm/s)	5.8 (4.7-6.9)	5.9 (4.7-7.1)	5.2 (4.3-6.4)	0.002
E/e' ratio	12 (9-14)	12 (9-14)	13 (10-17)	0.012
E/A ratio	0.9 (0.8-1.1)	0.9 (0.8-1.1)	0.9 (0.7-1.0)	0.002
Deceleration time (ms)	218 (171-271)	208 (170-271)	211 (179-264)	0.165
Left ventricular global longitudinal strain (%)	-15.1 ± 3.2	-15.3 ± 3.2	-13.9 ± 3.2	<0.001
Left ventricular global longitudinal strain at endocardium (%)	-17.5 ± 3.6	-17.7 ± 3.6	-16.5 ± 3.7	0.005
Left ventricular global longitudinal strain at mid-myocardium (%)	-15.3 ± 3.2	-15.6 ± 3.2	-14.2 ± 3.2	<0.001
Left ventricular global longitudinal strain at epicardium (%)	-13.2 ± 2.9	-13.4 ± 2.8	-11.9 ± 2.8	<0.001

Data are presented as mean ± standard deviation, number (percentage) or as median (25^{th}-75^{th} percentile). p-values are presented for the comparisons between different groups.

A total of 95 patients (17%) died during a median follow-up of 117 (IQR 106-132) months. The Kaplan-Meier curves for all-cause mortality according to each layer-specific LV GLS are shown in Figure 2. The population was divided into two groups according the median LV GLS of each individual layer. The cumulative survival rates were significantly higher for patients with preserved LV GLS (more negative) at the mid-myocardium (≤-15.3%; $\chi2 = 4.2$, log-rank p = 0.041) and the epicardium (≤-13.0%; $\chi2 = 8.8$, log-rank p = 0.003). On univariable Cox regression analysis, associates of all-cause mortality were age, male sex, body mass index, heart rate at discharge, eGFR, Killip class ≥2, multi-vessel disease, end-diastolic volume and end-systolic volume. Subsequently, on multivariable analysis only age remained independently associated with all-cause mortality (Table 3). To investigate the independent association of multi-layer global longitudinal strain, 3 different models were developed, each of them including one of the LV layers. The correlation coefficient between each LV layer-specific GLS was >0.7 (endocardial vs. mid-myocardium; r = 0.991, p<0.001), (endocardial vs. epicardium; r = 0.954, p <0.001) and (mid-myocardium vs. epicardium; r = 0.985, p <0.001). Therefore, to avoid multicollinearity these variables were not forced into the same multivariate model and were introduced in 3 separate multivariate models with similar baseline variables. On multivariable analysis, increasing age and epicardial LV GLS (HR = 1.085; [95%CI; 1.001 to 1.175], p = 0.047) were independently associated with all-cause mortality (Table 4). To determine the incremental value of layer-specific LV GLS over clinical and conventional echocardiographic parameters, global $\chi2$ values were calculated using cox regression models (Table 4). The addition of layer-specific LV GLS to the baseline model resulted in a significant increase in $\chi2$ values only for LV GLS measured at the epicardium (Figure 3).

Discussion

The main findings of the present study can be summarized as follows: in a homogenous contemporary STEMI population with mildly reduced or preserved LVEF, patients who died during follow-up had more impaired LV GLS at all layers (endomyocardial, mid-myocardial and epicardial, reflecting more extensive scar tissue) at baseline echocardiography when compared to their counterparts. In

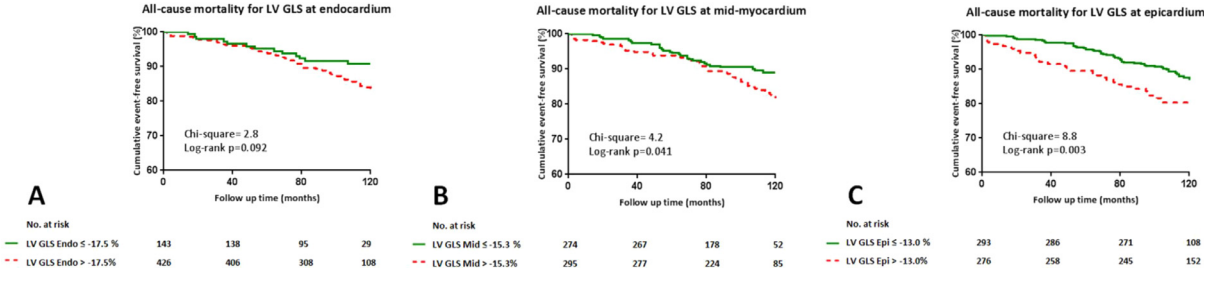

Figure 2. Kaplan-Meier curves for all-cause mortality according multilayer left ventricular global longitudinal strain. Panel A: demonstrates the survival for patients according to median left ventricular GLS at the endocardium. Panel B: demonstrates the survival for patients according to median left ventricular GLS at the mid-myocardium. Panel C: demonstrates the survival for patients according to median left ventricular GLS at the epicardium. Endo = endocardium; Epi = epicardium; GLS = global longitudinal strain; LV = left ventricular; mid = mid-myocardium.

Table 3
Univariable and multivariable Cox proportional hazard models for all-cause mortality

Variable	Univariable analysis			Model 1 (baseline model)		
	HR	95% CI	p value	HR	95% CI	p value
Age (years)	1.106	1.083-1.129	<0.001	1.098	1.071-1.125	<0.001
Gender (male)	1.550	1.006-2.390	0.047	0.723	0.428-1.222	0.226
Body mass, indexed (kg/m^2)	0.933	0.878-0.991	0.024	0.961	0.898-1.028	0.247
Heart rate, at discharge	1.019	1.003-1.036	0.017	1.010	0.992-1.028	0.290
iabetes mellitus	1.548	0.852-3.902	0.174	—	—	—
Angiotensin converting enzyme inhibitors/ Angiotensin receptor blockers, at discharge	0.659	0.241-1.797	0.415	—	—-	—
β-blockers, at discharge	0.775	0.339-1.773	0.546	—	—	—
Peak cardiac troponin T (μg/L), at baseline	1.006	0.967-1.045	0.778	—	—	—
eGFR (ml/min/1.73m^2), at baseline	0.981	0.973-0.988	<0.001	0.994	0.987-1.002	0.126
Left anterior descending coronary artery as culprit vessel	1.137	0.748-1.728	0.548	—	—	—
Killip class ≥2, at baseline	3.696	1.915-7.134	<0.001	1.569	0.722-3.408	0.255
Multi-vessel disease, at baseline	1.590	1.060-2.385	0.025	1.017	0.657-1.575	0.940
Left ventricular ejection fraction (%), at baseline	0.992	0.959-1.027	0.666	—	—	—
Left ventricular end-diastolic diameter (mm), at baseline	0.989	0.982-0.996	0.001	0.995	0.983-1.008	0.462
Left ventricular end-systolic diameter (mm), at baseline	0.985	0.972-0.997	0.019	1.009	0.986-1.033	0.447
Wall motion score index, at baseline	1.041	0.472-2.296	0.921	—	—	—
Mitral regurgitation ≥2, at baseline	1.154	0.827-1.611	0.398	—	—	—
Left ventricular mass (indexed), at baseline	1.003	0.996-1.010	0.443	—	—	—

CI = confidence interval; HR = hazard ratio

Table 4
Multivariable analysis to investigate the incremental value of layer-specific LV GLS for all-cause mortality

Baseline values	Model 2(Model 1 + LV GLS endocardium)			Model 3(Model 1 + LV GLS mid-myocardium)			Model 4(Model 1 + LV GLS epicardium)		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Age (years)	1.097	1.070-1.125	**<0.001**	1.098	1.070-1.126	**<0.001**	1.095	1.068-1.123	**<0.001**
Man	0.711	0.420-1.204	0.204	0.713	0.420-1.209	0.209	0.723	0.427-1.224	0.227
Body mass, indexed (kg/m^2)	0.963	0.900-1.031	0.278	0.969	0.906-1.038	0.371	0.966	0.902-1.035	0.325
Heart rate, at discharge (bpm)	1.008	0.990-1.026	0.399	1.007	0.989-1.025	0.466	1.005	0.987-1.024	0.561
eGFR (ml/min/1.73m^2)	0.994	0.987-1.002	0.123	0.994	0.987-1.002	0.146	0.994	0.987-1.002	0.142
Killip class ≥2	1.585	0.728-3.450	0.246	1.578	0.725-3.435	0.250	1.553	0.714-3.382	0.267
Multi-vessel coronary disease	1.008	0.650-1.563	0.972	0.969	0.622-1.508	0.888	1.000	0.644-1.553	1.000
Left ventricular end-diastolic diameter (mm)	0.996	0.982-1.009	0.509	0.995	0.982-1.008	0.419	0.997	0.983-1.010	0.619
Left ventricular end-systolic diameter (mm)	1.007	0.983-1.032	0.549	1.009	0.985-1.033	0.480	1.005	0.981-1.030	0.676
Left ventricular global longitudinal strain at endocardium (%)	1.030	0.969-1.095	0.345	—	—	—	—	—	—
Left ventricular global longitudinal strain at mid-myocardium (%)	—	—	—	1.057	0.985-1.134	0.126	—	—	—
Left ventricular global longitudinal strain at epicardium (%)	—	—	—	—	—	—	1.085	1.001-1.175	**0.047**

CI= confidence interval; HR= hazard ratio

contrast, we observed no differences in enzymatic infarct size nor LVEF between survivors and non-survivors. Furthermore, multivariable analysis demonstrated that aging and reduced LV GLS of the epicardial layer (reflecting transmural infarction) were independently associated with higher risk of all-cause mortality. Finally, reduced LV GLS at the epicardium shows significant incremental value for prediction of all-cause mortality after adjusting for clinical, biological and echocardiographic variables.

In current clinical practise, echocardiography plays a central role in the evaluation of regional and global LV systolic function after acute myocardial infarction.[1] LV systolic function (before hospital discharge) remains an important predictor of survival in patients after acute myocardial infarction.[1] Currently, contemporary guidelines recommend LVEF assessment, and not LV GLS, as the main measurement of LV systolic function in patients after acute myocardial infarction.[10] However, LV GLS has been shown to be superior over LVEF in terms of reproducibility and prediction of hard events such as all-cause and cardiovascular mortality.[4] In addition, LV GLS is a more sensitive measure of LV systolic dysfunction and may be impaired while LVEF is still within the normal range.[15,16] It has been hypothesized that an increase in radial and circumferential strain may compensate for reduced longitudinal strain (as longitudinal strain

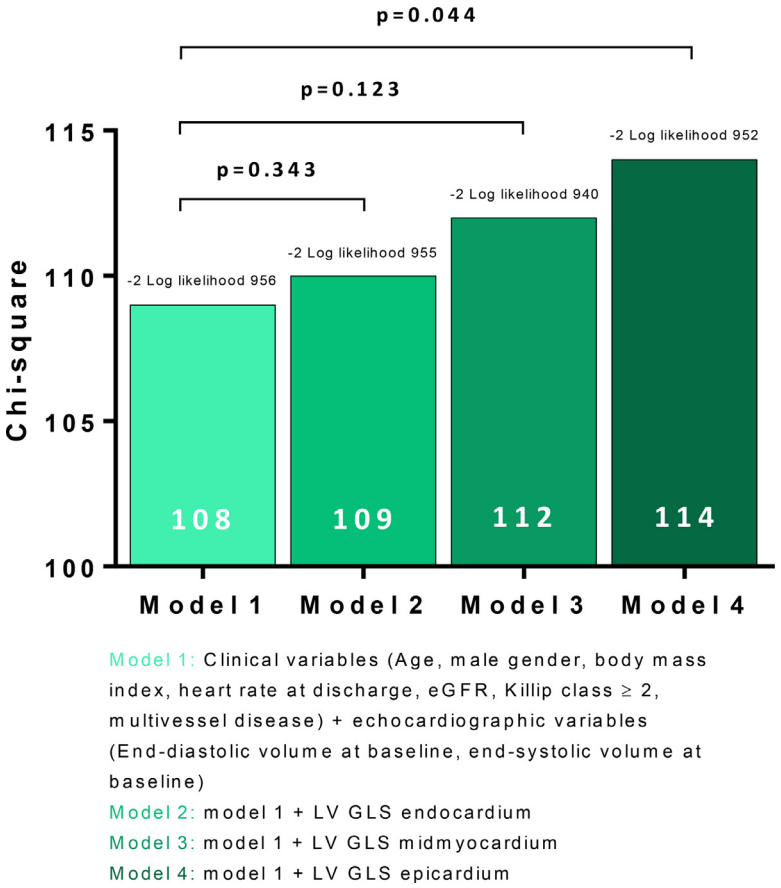

Figure 3. The incremental value of multilayer left ventricular global longitudinal strain over baseline clinical and echocardiographic variables associated with all-cause mortality.

is more prone to myocardial injury) and therefore LVEF remains preserved.[17,18] Therefore, LV GLS is considered a more sensitive marker of LV systolic dysfunction when compared to traditional echocardiographic parameters such as LVEF.

Layer-specific LV GLS allows for a more comprehensive understanding of LV systolic function.[19-21] Several studies have shown the clinical value of layer-specific LV GLS in patients with coronary artery disease.[22-24] Similar, conflicting results are reported on which layer yields the best prognostic value. Hamada et al[25] showed in a study including 390 patients with chronic ischemic cardiomyopathy that LV GLS and particularly global circumferential strain at the endocardium was associated with adverse cardiac events (readmission, worsening of heart failure, ventricular arrhythmias or all-cause mortality) independent of LVEF and transmural scar assessed on cardiac magnetic resonance. However a recent study by Skaarup et al,[7] including 465 patients after acute coronary syndrome (STEMI, non-STEMI and unstable angina) demonstrated that LV GLS measured at all layers was associated with adverse events (heart failure and cardiovascular death). In addition, only LV GLS and LV GLS at the epicardium displayed stronger prognostic power for adverse events after adjusting for clinical and echocardiographic parameters. Furthermore, only LV GLS at the epicardium remained independently associated with cardiac death.

Similar to our study, both Hamada et al[25] and Skaarup et al[7] report a gradient over the LV myocardial wall with a decrease from the endocardium to the epicardium. However, our study provides additional evidence in a relatively large homogenous STEMI population treated according current guidelines.[26,27] Similar to the study by Skaarup et al,[7] we report that both LV GLS measured at midmyocardium and at the epicardium are associated with mortality. However, on multivariable analysis, only LV GLS at the epicardium remained associated with all-cause mortality (suggestion more transmural scar formation). Interestingly, it has been suggested that a layer-specific analysis may aid to discriminate between transmural vs subendocardial infarction. As the endocardium plays an important role in discriminating non-infarcted areas from non-transmural areas, the epicardium discriminates better between the non-transmural areas and transmural areas.[28] Whereas the LV endocardial orientated fibers are primarily affected in ischemic heart disease and largely responsible for the longitudinal function,[5] the mid-myocardium and the epicardial layer mostly contribute to thickening and to radial and circumferential LV systolic function. Therefore, more preserved mid-myocardium and epicardial layers appear to prevent further LV deterioration, as they reflect the extent of affected LV myocardial tissue.[29,30]

Several limitations should be acknowledged. The current study was retrospective in nature and all data were

generated from a single centre. Furthermore, we have not examined any alteration in medical management during follow up. Finally, the measurements of layer-specific LV GLS may not be generalizable for all vendors and the cut-off value of layer-specific LV GLS provided in this study may not be applicable in other study populations.

Authors Contribution

Rachid Abou: conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; validation; visualization; writing - originaldraft. Laurien Goedemans: conceptualization; data curation; formal analysis; investigation; methodology; resources; validation; writing & editing. José M. Montero-Cabezas: conceptualization; datacuration; methodology; resources; validation; writing & editing. Edgard A. Prihadi: conceptualization; datacuration; methodology; resources; validation; writing & editing. Mohammed el Mahdiui: conceptualization; datacuration; methodology; resources; validation; writing & editing. Martin J. Schalij: conceptualization; datacuration; methodology; resources; validation; writing & editing. Nina Ajmone Marsan: conceptualization; funding acquisition; methodology; project administration; supervision; validation; writing & editing. Victoria Delgado: conceptualization; data curation; funding acquisition; methodology; project administration; resources; supervision; validation; writing & editing. Jeroen J. Bax: conceptualization; data curation; funding acquisition; methodology; project administration; resources; supervision; validation; writing & editing

Conflict of Interest

Victoria Delgado received speaker fees from Abbott Vascular, Medtronic, Edwards Lifesciences, MSD, Novartis and GE Healthcare. Jeroen J Bax and Nina Ajmone Marsan received speaker fees from Abbott Vascular. The Department of Cardiology of the Leiden University Medical Center received unrestricted research grants from Abbott Vascular, Bayer, Biotronik, Bioventrix, Medtronic, Boston Scientific Corporation, GE Healthcare and Edwards Lifesciences. The remaining authors have nothing to disclose.

1. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;39:119–177.
2. Baron T, Flachskampf FA, Johansson K, Hedin EM, Christersson C. Usefulness of traditional echocardiographic parameters in assessment of left ventricular function in patients with normal ejection fraction early after acute myocardial infarction: results from a large consecutive cohort. *Eur Heart J Cardiovasc Imaging* 2016;17:413–420.
3. Marwick TH. Ejection fraction pros and cons: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2018;72:2360–2379.
4. Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. *Heart (British Cardiac Society)* 2014;100:1673–1680.
5. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 1977;56:786–794.
6. Altiok E, Neizel M, Tiemann S, Krass V, Becker M, Zwicker C, Koos R, Kelm M, Kraemer N, Schoth F, Marx N, Hoffmann R. Layer-specific analysis of myocardial deformation for assessment of infarct transmurality: comparison of strain-encoded cardiovascular magnetic resonance with 2D speckle tracking echocardiography. *Eur Heart J Cardiovasc Imaging* 2013;14:570–578.
7. Skaarup KG, Iversen A, Jorgensen PG, Olsen FJ, Grove GL, Jensen JS, Biering-Sorensen T. Association between layer-specific global longitudinal strain and adverse outcomes following acute coronary syndrome. *Eur Heart J Cardiovasc Imaging* 2018;19:1334–1342.
8. Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. *JACC Cardiovasc Imaging* 2018;11:260–274.
9. Liem S-S, van der Hoeven BL, Oemrawsingh PV, Bax JJ, van der Bom JG, Bosch J, Viergever EP, van Rees C, Padmos I, Sedney MI, van Exel HJ, Verwey HF, Atsma DE, van der Velde ET, Jukema JW, van der Wall EE, Schalij MJ. MISSION!: optimization of acute and chronic care for patients with acute myocardial infarction. *Am Heart J* 2007;153. 14.e11-14.e11.
10. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233–270.
11. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, Badano L, Zamorano JL. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013;14:611–644.
12. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016;17:1321–1360.
13. Negishi K, Negishi T, Kurosawa K, Hristova K, Popescu BA, Vinereanu D, Yuda S, Marwick TH. Practical guidance in echocardiographic assessment of global longitudinal strain. *JACC Cardiovas Imaging* 2015;8:489–492.
14. Abou R, Leung M, Khidir MJH, Wolterbeek R, Schalij MJ, Ajmone Marsan N, Bax JJ, Delgado V. Influence of aging on level and layer-specific left ventricular longitudinal strain in subjectsWithout structural heart disease. *Am J Cardiol* 2017;120:2065–2072.
15. Tops LF, Delgado V, Marsan NA, Bax JJ. Myocardial strain to detect subtle left ventricular systolic dysfunction. *Eur J Heart Fail* 2017;19:307–313.
16. Ng AC, Delgado V, Bertini M, van der Meer RW, Rijzewijk LJ, Hooi Ewe S, Siebelink HM, Smit JW, Diamant M, Romijn JA, de Roos A, Leung DY, Lamb HJ, Bax JJ. Myocardial steatosis and biventricular strain and strain rate imaging in patients with type 2 diabetes mellitus. *Circulation* 2010;122:2538–2544.
17. Biering-Sorensen T, Santos M, Rivero J, McCullough SD, West E, Opotowsky AR, Waxman AB, Systrom DM, Shah AM. Left ventricular deformation at rest predicts exercise-induced elevation in pulmonary artery wedge pressure in patients with unexplained dyspnoea. *Eur J Heart Fail* 2017;19:101–110.
18. Biering-Sorensen T, Solomon SD. Assessing contractile function when ejection fraction is normal: a case for strain imaging. *Circ Cardiovasc Imaging* 2015;8:e004181.
19. Shi J, Pan C, Kong D, Cheng L, Shu X. Left ventricular longitudinal and circumferential layer-specific myocardial strains and their determinants in healthy subjects. *Echocardiography* 2015;33:510–518.
20. Abou R, Leung M, Khidir MJH, Wolterbeek R, Schalij MJ, Ajmone Marsan N, Bax JJ, Delgado V. Influence of aging on level and layer-specific left ventricular longitudinal strain in subjects without structural heart disease. *Am J Cardiol* 2017;120:2065–2072.

21. Leitman M, Lysiansky M, Lysyansky P, Friedman Z, Tyomkin V, Fuchs T, Adam D, Krakover R, Vered Z. Circumferential and longitudinal strain in 3 myocardial layers in normal subjects and in patients with regional left ventricular dysfunction. *J Am Soc Echocardiogr* 2010;23:64–70.
22. Sarvari SI, Haugaa KH, Zahid W, Bendz B, Aakhus S, Aaberge L, Edvardsen T. Layer-specific quantification of myocardial deformation by strain echocardiography may reveal significant CAD in patients with non-ST-segment elevation acute coronary syndrome. *JACC Cardiovasc Imaging* 2013;6:535–544.
23. Zhang L, Wu WC, Ma H, Wang H. Usefulness of layer-specific strain for identifying complex CAD and predicting the severity of coronary lesions in patients with non-ST-segment elevation acute coronary syndrome: compared with Syntax score. *Int J Cardiol* 2016;223:1045–1052.
24. Hagemann CE, Hoffmann S, Olsen FJ, Jorgensen PG, Fritz-Hansen T, Jensen JS, Biering-Sorensen T. Layer-specific global longitudinal strain reveals impaired cardiac function in patients with reversible ischemia. *Echocardiography* 2018;35:632–642.
25. Hamada S, Schroeder J, Hoffmann R, Altiok E, Keszei A, Almalla M, Napp A, Marx N, Becker M. Prediction of outcomes in patients with chronic ischemic cardiomyopathy by layer-specific strain echocardiography: a proof of concept. *J Am Soc Echocardiogr* 2016;29:412–420.
26. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;33:2569–2619.
27. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX. 2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol* 2013;61:e78–e140.
28. Becker M, Ocklenburg C, Altiok E, Futing A, Balzer J, Krombach G, Lysyansky M, Kuhl H, Krings R, Kelm M, Hoffmann R. Impact of infarct transmurality on layer-specific impairment of myocardial function: a myocardial deformation imaging study. *Eur Heart J* 2009;30:1467–1476.
29. Hung CL, Verma A, Uno H, Shin SH, Bourgoun M, Hassanein AH, McMurray JJ, Velazquez EJ, Kober L, Pfeffer MA, Solomon SD. Longitudinal and circumferential strain rate, left ventricular remodeling, and prognosis after myocardial infarction. *J Am Coll Cardiol* 2010;56:1812–1822.
30. Abate E, Hoogslag GE, Leong DP, Bertini M, Antoni ML, Nucifora G, Joyce E, Holman ER, Siebelink HM, Schalij MJ, Bax JJ, Delgado V, Ajmone Marsan N. Association between multilayer left ventricular rotational mechanics and the development of left ventricular remodeling after acute myocardial infarction. *J Am Soc Echocardiogr* 2014;27:239–248.