Five-Year Outcomes and Prognostic Value of Feature-Tracking Cardiovascular Magnetic Resonance in Patients Receiving Early Prereperfusion Metoprolol in Acute Myocardial Infarction

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The aim of the present study was to investigate the long-term impact of early intravenous metoprolol in ST-segment elevation myocardial infarction (STEMI) patients in terms of left ventricular (LV) strain with feature-tracking cardiovascular magnetic resonance (CMR) and its association with prognosis. A total of 270 patients with first anterior STEMI enrolled in the randomized METOCARD-CNIC clinical trial, assigned to receive up to 15 mg intravenous metoprolol before primary percutaneous coronary intervention versus conventional STEMI therapy, were included. LV global circumferential (GCS) and longitudinal (GLS) strain were assessed with feature-tracking CMR at 1 week after STEMI in 215 patients. The occurrence of major adverse cardiac events (MACE) at 5-year follow-up was the primary end point. Among 270 patients enrolled, 17 of 139 patients assigned to metoprolol arm and 31 of 131 patients assigned to control arm experienced MACE (hazard ratio [HR] 0.500, 95% confidence interval [CI] 0.277 to 0.903; p = 0.022). Impaired LV GCS and GLS strain were significantly associated with increased occurrence of MACE (GCS: HR 1.208, 95% CI 1.076 to 1.356, p =0.001; GLS: HR 1.362, 95% CI 1.180 to 1.573, p < 0.001). On multivariable analysis, LV GLS provided incremental prognostic value over late gadolinium enhancement (LGE) and LV ejection fraction (LVEF) (LGE + LVEF chi-square = 12.865, LGE + LVEF + GLS chi-square = 18.459; p =0.012). Patients with GLS ≥-11.5% (above median value) who received early intravenous metoprolol were 64% less likely to experience MACE than their counterparts with same degree of GLS impairment (HR 0.356, 95% CI 0.129 to 0.979; p = 0.045). In conclusion, early intravenous metoprolol has a long-term beneficial prognostic effect, particularly in patients with severely impaired LV systolic function. LV GLS with feature-tracking CMR early after percutaneous coronary intervention offers incremental prognostic value over conventional CMR parameters in risk stratification of STEMI patients. **(Am J Cardiol 2020;133:39−47)**

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The outcome of patients with ST-segment elevation myocardial infarction (STEMI) has significantly improved over the last decades.[1,2] However, STEMI survivors are still at high risk of recurrent cardiovascular events such as congestive heart failure, arrhythmia, and sudden death.[3,4] In the acute phase of STEMI, novel therapeutic approaches aiming at reducing the ischemia-reperfusion injury are being tested.[5,6] The beneficial effect of early intravenous β-blockade in STEMI population was demonstrated in the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial[7,8] and was adopted by current guidelines.[3] Recently, the impact of multidirectional left ventricular (LV) strain with feature-tracking cardiovascular magnetic resonance (CMR) has been studied in STEMI patients.[9−14] Conflicting results with respect to the incremental value of feature-tracking CMR over traditional markers of infarct injury, such as LV ejection fraction (LVEF) and infarct size with late gadolinium enhancement (LGE), have been observed.[9−14] The current analysis aims at addressing 3 questions (1) whether early intravenous metoprolol offers a long-term beneficial effect in STEMI patients over a 5-year follow-up, (2) whether LV global circumferential (GCS) and longitudinal (GLS) strain with feature-tracking CMR show incremental prognostic value over conventional CMR parameters in STEMI patients and (3) whether the association between global LV strain and prognosis is modulated by early intravenous metoprolol treatment.

Methods

The METOCARD-CNIC trial was a multicenter, randomized, parallel-group, single-blinded (to outcome evaluators) clinical trial (ClinicalTrials.gov identifier: NCT01311700). The study design and protocol have been previously described.[15] Briefly, a total of 270 patients with first anterior STEMI were randomized to receive up to 15 mg intravenous metoprolol before primary percutaneous coronary intervention versus conventional therapy. Patients presenting with Killip class III to IV acute heart failure, systolic blood pressure persistently <120 mm Hg, PR interval >240 milliseconds (or type II to III atrioventricular block), heart rate persistently <60 beats/min, or active treatment with any β-blocker agent were excluded from the trial. All patients, including those in control arm, received oral metoprolol (first dose 12 to 24 hours after reperfusion). CMR was performed in 220 patients at 1 week (5 to 7 days) after STEMI. There were no differences in demographic variables, cardiovascular risk profile and procedural characteristics between patients receiving early intravenous metoprolol and the controls.[7] The study was approved by the ethical committees and institutional review boards at each participating center. All eligible patients gave written informed consent.

The CMR data acquisition was performed with 1.5 and 3.0 T CMR scanners. The 2-, 3- and 4-chamber views and a stack of contiguous short-axis slices to cover the whole LV were acquired with steady-state free precession functional cine imaging. Data acquisition parameters were: voxel size 1.6×2 mm, slice thickness 8 mm, gap 0 mm, cardiac phases 25-30, TR 3.5, TE 1.7, flip angle 40, SENSE 1.5, averages 1, FOV 360×360 mm. Segmented inversion recovery gradient echo sequence, acquired 10 to 15 minutes after a cumulative dose of 0.2 mmol/kg intravenous gadolinium contrast agent was employed for myocardial necrosis/fibrosis imaging. CMR data were analyzed with dedicated software (QMass MR 7.5; Medis, Leiden, the Netherlands) as described before.[15] LVEF was determined from the short-axis cine images with LV trabeculations included within the blood pool. LGE was quantified according to full-width-half-maximum method from short-axis delayed enhancement images and expressed as the percent of LV mass. The presence of microvascular obstruction (MVO), defined as hypointense areas within the hyperenhanced zone on LGE images, was evaluated.

Feature-tracking CMR analysis was performed with dedicated software (cvi[42] v5.3, Circle Cardiovascular Imaging, Calgary, Canada). First, the LV endo- and epicardium were manually delineated at end-diastole in short-axis and 2-, 3- and 4-chamber long-axis views. In addition, the anterior right ventricular insertion point, the mitral annulus and the LV apex were defined. Short-axis slices covering the whole LV were included in GCS analysis. Subsequently, the outlined myocardium borders were automatically tracked throughout the cardiac cycle with fully automated feature-tracking analysis. The quality of the myocardium tracking was visually evaluated with manual adjustments of the contours if necessary. Global time-strain curves were obtained and peak GCS and GLS values were recorded.

The primary end point of the present analysis was the occurrence of major adverse cardiac events (MACE) at 5-year follow-up after STEMI. MACE was defined as the composite of death, rehospitalization for heart failure, reinfarction, and malignant ventricular arrhythmias (ventricular fibrillation, sustained ventricular tachycardia), as in the prespecified METOCARD-CNIC trial end point.[15] Readmissions because of the heart failure were due to heart failure decompensation or due to the indication for implantable cardioverter defibrillator therapy. Clinical follow-up was performed by telephone interview and access to hospital reports. Clinical events for the 2-year follow-up[8] were blindly adjudicated by a committee but the extended follow-up events were not adjudicated. Some events were self-reported by the patient and in other cases a discharge report was available. To evaluate the prognostic influence of LV strain on outcomes, only the events occurring after the first CMR scan, that is, 1 week after STEMI, were included. In particular, all malignant ventricular arrhythmias occurred earlier and were not included in the analysis.

Normally distributed continuous variables are presented as mean and standard deviation and compared using independent samples t tests. Non-normal data are reported as medians, first and third quartiles and were compared with Mann-Whitney U test. Categorical variables are presented as counts and percentages and compared using the Pearson's Chi-square test. For the primary end point analysis, patients were censored at the occurrence of the first event. The impact of early intravenous metoprolol in the overall METOCARD-CNIC trial population was evaluated with Kaplan-Meier method and with Cox proportional hazards regression model. Subsequently, Cox regression analysis was performed in the cohort with available 1-week

CMR scan to identify the conventional and feature-tracking CMR variables associated with the primary end point. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated and adjusted for demographic and clinical variables. To evaluate the incremental prognostic value of LV GCS and GLS over the conventional CMR parameters, nested regression models were created and the global Chi-square values were compared. To investigate if patient prognosis was modulated by the interaction between global LV strain and early intravenous metoprolol treatment, patients were divided according to the median GCS and GLS values and the randomization status (early intravenous metoprolol vs. control group). The cumulative event rates were estimated using Kaplan-Meier survival curves. In addition, exploratory Cox regression analysis was performed to compare the HR for the occurrence of primary end point between individual groups. A 2-sided p-value of <0.05 was statistically significant. All statistical analyses were performed using IBM SPSS Statistics 23 (IBM, Armonk, New York).

Results

In the overall METOCARD-CNIC trial population of 270 patients (139 treated with early intravenous metoprolol and 131 with conventional STEMI therapy) 214 patients (79.3%) completed the 5-year follow-up and 48 patients (17.8%) presented with MACE (Figure 1). Patients who received early intravenous metoprolol had fewer cumulative MACE (HR 0.500, 95% CI 0.277 to 0.903; $p = 0.022$) and fewer heart failure admissions (HR 0.298, 95% CI 0.096 to 0.924; $p = 0.036$; Table 1). The Kaplan-Meier curves for the occurrence of MACE in both treatment arms are shown in Figure 2.

Among 220 patients who underwent 1-week CMR scan, feature-tracking analysis was feasible in 215 patients (early metoprolol group: N = 105 of 106; control group: N = 110 of 114) and they formed the population for the LV strain analysis (Figure 1). A total of 185 patients (86.0%) completed the 5-year follow-up and 25 patients (11.6%) presented with MACE. Patients experiencing MACE had higher body mass index, were more often diabetic and had more pronounced LV systolic dysfunction (demonstrated by impaired LVEF, GCS, and GLS) and greater infarct size 1 week after STEMI compared with patients without MACE (Table 2). On univariable Cox regression analysis, LV CMR imaging parameters (except for MVO) were significantly associated with the occurrence of the primary endpoint (Table 3). Each 1% increase in LV GCS was associated with 21% increased risk of MACE whereas each 1% increase in LV GLS was associated with 36% increased risk of MACE. After adjusting for demographic and clinical variables, the association between LV GCS and GLS with the occurrence of MACE remained statistically significant (Table 3). Moreover, after adjusting for demographic and clinical variables also MVO was significantly associated with the occurrence of the primary endpoint. To assess the incremental prognostic value of GCS and GLS over conventional CMR parameters, nested regression models were created and global chi-square values were calculated (Figure 3). Adding GLS to a model including LGE and LVEF significantly increased the chi-square value (LGE + LVEF chi-square = 12.865, LGE + LVEF + GLS chi-square = 18.459; $p = 0.012$). In contrast, the addition of LV GCS or MVO to the model including LGE and LVEF did not have statistically significant incremental prognostic value.

To explore the interaction between LV GCS and GLS and the effect of early intravenous metoprolol, 215 patients with 1-week CMR feasible for feature-tracking analysis (the LV strain population) were divided into 4 groups according to the median LV GCS (−13.1%; interquartile range −10.0% to −16.5%) and GLS values (−11.5%; interquartile range −9.4% to −13.4%) and the randomization status (early intravenous metoprolol vs. conventional therapy). The crude event rates in each patient group are presented in Table 4. The Kaplan-Meier curves show significant differences between groups for the cumulative MACE (Figure 4). Patients with more impaired strain who were treated with conventional STEMI therapy had the highest event rates while the differences between other 3 groups were less pronounced. In the exploratory subgroup analysis, patients with more impaired GLS (≥−11.5%) who received early intravenous metoprolol were 64% less likely to experience MACE (HR 0.356, 95% CI 0.129 to 0.979; $p = 0.045$) than their counterparts with same degree of GLS impairment but receiving conventional STEMI therapy. A similar, but not statistically significant trend was observed for patients with more impaired GCS (≥−13.1%) (HR for early metoprolol treatment 0.400, 95% CI 0.132 to 1.216; $p = 0.106$).

Discussion

The present study demonstrated that (1) early intravenous metoprolol has a long-term beneficial prognostic value in STEMI patients, (2) LV GLS measured with feature-tracking CMR early after STEMI provides incremental prognostic value over LVEF and infarct size assessed with LGE, and (3) the association between GCS, GLS, and prognosis is modulated by early intravenous metoprolol treatment with the majority of MACE occurring in patients with impaired LV strain treated with conventional STEMI therapy.

The METOCARD-CNIC trial was the first randomized control trial in the modern era of primary PCI in STEMI that evaluated the cardioprotective effect of intravenous β-blockers.[7] Early intravenous administration of metoprolol (before primary PCI) was associated with significant reduction of primary end point, the infarct size measured with LGE CMR 1 week after STEMI.[7] In addition, early intravenous metoprolol administration was associated with a non-significant trend toward reduced occurrence of prespecified MACE (10.8% in the metoprolol group vs 18.3% in the control group; $p = 0.065$) and a significant reduction in heart failure readmissions (2.2% in the metoprolol group vs 6.9% in the control group; $p = 0.046$) at a median follow-up of 2 years.[8] In the present article, the impact of early intravenous metoprolol treatment in the METOCARD-CNIC trial population was reinvestigated with extended 5-year follow-up data and significant reduction in both, MACE as well as heart failure readmissions, was demonstrated. In addition,

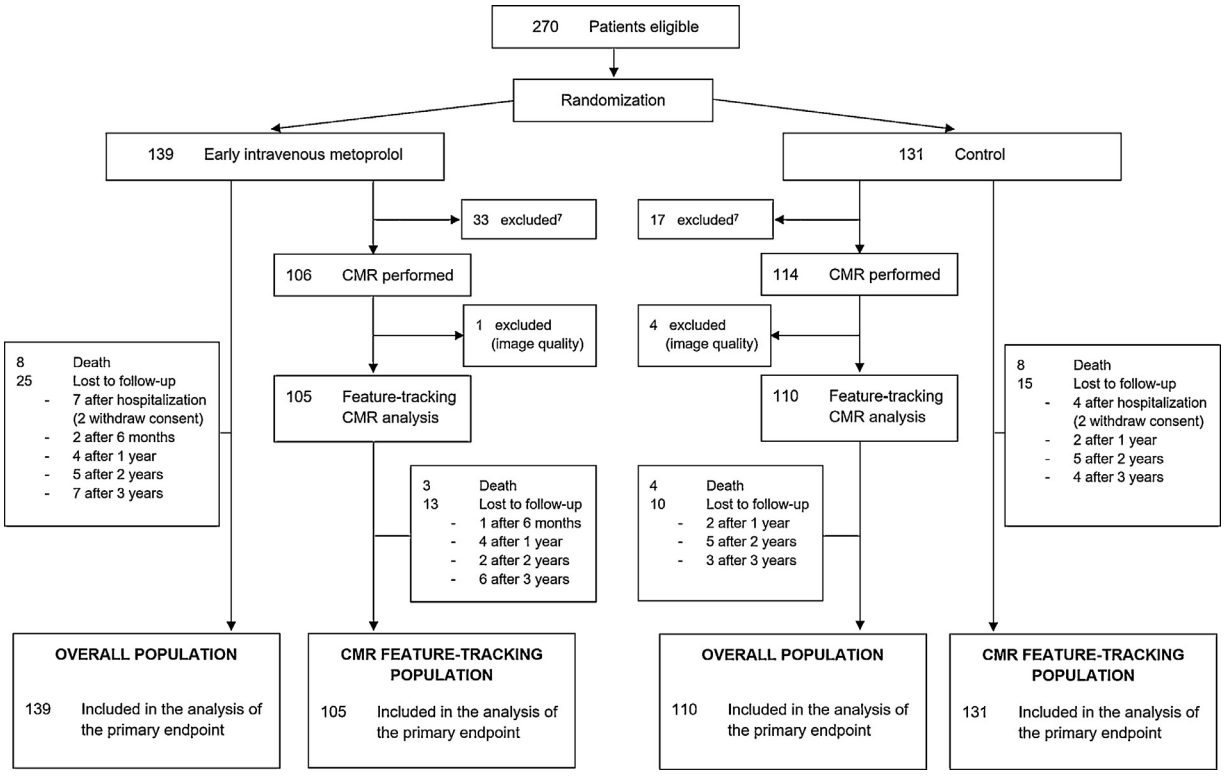

Figure 1. Study flow diagram. CMR = cardiovascular magnetic resonance.

Table 1
The occurrence of MACE in patients according to the randomization status in the overall METOCARD-CNIC trial population

	Metoprolol (N = 139)	Control (N = 131)	HR (95% CI)	p Value
MACE*	17 (12.2%)	31 (23.7%)	0.500 (0.277-0.903)	0.022
Death	8 (5.8%)	8 (6.1%)	0.903 (0.339-2.405)	0.838
Cardiac death	3 (2.2%)	6 (4.6%)		
Noncardiac death†	5 (3.6%)	2 (1.5%)		
HF admission	4 (2.9%)	12 (9.2%)	0.298 (0.096-0.924)	0.036
Reinfarction	1 (0.7%)	5 (3.8%)	0.179 (0.021-1.536)	0.117
Malignant ventricular arrhythmia	5 (3.6%)	10 (7.6%)	0.477 (0.163-1.397)	0.177

CI = confidence interval; HF = heart failure; HR = hazard ratio; MACE = major adverse cardiac events.
* A few patients experienced more than 1 event, however in MACE only the first event was included.
† Among noncardiac deaths 6 were due to cancer and 1 due to hemoptysis (metoprolol group).

we have previously shown that patients who received early intravenous metoprolol had more preserved global LV strain and infarct zone circumferential strain after STEMI.[16,17] However, in the present analysis we have demonstrated that patients with impaired LV strain, particularly those with impaired GLS, who were treated with early intravenous metoprolol had lower adverse event rates than their counterparts with same degree of LV strain impairment but receiving conventional STEMI therapy. These results strengthen our current evidence of the beneficial long-term prognostic effect of early intravenous metoprolol in STEMI patients with primary PCI and without contraindications to β-blockers.

In recent years, several CMR techniques have emerged to assess regional and global LV systolic function in patients with acute myocardial infarction.[18] Among these techniques, feature-tracking CMR has gained prominence as a fast and accurate modality for the assessment of LV strain using standard cine images. Recently, the association between multidirectional LV strain with feature-tracking CMR after myocardial infarction and patients outcome has been explored in 4 large patient cohorts.[9–12] Eitel et al[9] included 1,107 patients after myocardial infarction and demonstrated an incremental prognostic value of LV GLS for all-cause mortality but not for the occurrence of MACE, over LVEF and infarct size. Gavara et al[10] studied 323 patients after STEMI and showed that LV GLS rather than GCS or global radial strain was an independent predictor of MACE. However, in the multivariable models including clinical and CMR variables GLS did not significantly improve patients risk reclassification. Yoon et al[11] and Reindl et al[12] demonstrated incremental prognostic value of GLS with feature-tracking CMR over LVEF and CMR markers of infarct severity for the occurrence of MACE in

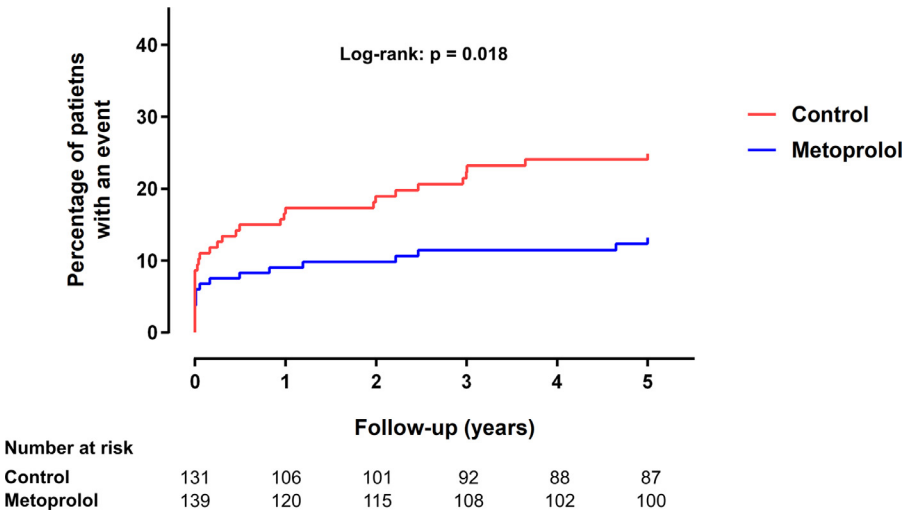

Figure 2. Kaplan Meier estimates for cumulative major adverse cardiac event rates in the overall METOCARD-CNIC trial population.

Table 2
Clinical and CMR characteristics of patients with feature-tracking CMR analysis

Variable	Overall (N = 215)	MACE (N = 25)	No MACE (N = 190)	p Value
Age (years)	58.4 ± 11.5	61.8 ± 9.1	57.9 ± 11.7	0.059
Men	187 (87%)	23 (92%)	164 (86%)	0.748
BMI (kg/m^2)	27.3 (25.4-29.4)	28.1 (27.5-30.9)	26.7 (25.2-29.3)	0.006
Hypertension	84 (39%)	14 (56%)	70 (37%)	0.071
Diabetes mellitus	42 (20%)	9 (36%)	33 (17%)	0.029
Smoker*	136 (63%)	15 (60%)	121 (64%)	0.670
LGE (%)	22.0±13.3	28.4±14.1	21.1±13.0	0.009
Presence of MVO	126 (59%)	19 (76%)	107 (56%)	0.068
LVEF (%)	44.9±9.8	38.6±9.3	45.8±9.5	0.001
LV GCS (%)	-13.5±4.0	-11.2±4.3	-13.8±3.9	0.002
LV GLS (%)	-11.6±3.2	-9.1±3.0	-11.9±3.1	<0.001

Values are mean ± SD, median (interquartile range) or n (%). BMI = body mass index; GCS = global circumferential strain; GLS = global longitudinal strain; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; MACE = major adverse cardiac event; MVO = microvascular obstruction.

* Smoker was defined as current or quitted <10 years ago.

Table 3
Clinical and CMR variables as predictors of the primary endpoint in patients with feature-tracking CMR analysis

Variable	Univariable analysis			Multivariable analysis*		
	HR	95% CI	p Value	HR	95% CI	p Value
Age (years)	1.026	0.991-1.063	0.140			
Men	1.696	0.400-7.195	0.473			
BMI (kg/m^2)	1.118	1.023-1.222	0.014			
Hypertension	2.088	0.948-4.599	0.068			
Diabetes mellitus	2.537	1.121-5.743	0.025			
Smoker†	0.831	0.373-1.850	0.650			
LGE (%)	1.040	1.009-1.071	0.010	1.046	1.014-1.078	0.004
Presence of MVO	2.261	0.903-5.662	0.081	2.801	1.081-7.257	0.034
LVEF (%)	0.922	0.882-0.965	<0.001	0.908	0.868-0.951	<0.001
GCS (%)	1.208	1.076-1.356	0.001	1.228	1.094-1.378	<0.001
GLS (%)	1.362	1.180-1.573	<0.001	1.372	1.184-1.589	<0.001

BMI = body mass index; CI = confidence interval; GCS = global circumferential strain; GLS = global longitudinal strain; HR = hazard ratio; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; MVO = microvascular obstruction.

* CMR variables were adjusted for demographic and clinical parameters (age, sex, BMI, hypertension, diabetes mellitus, smoking status).

† Smoker was defined as current or quitted <10 years ago.

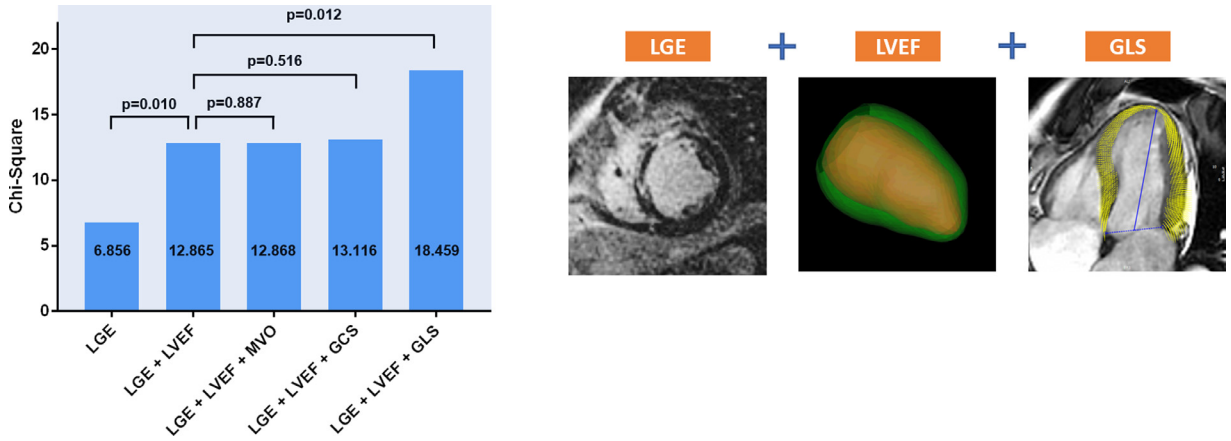

Figure 3. **Incremental prognostic value of left ventricular strain with feature-tracking CMR.** Bar graphs illustrate the prognostic value of cardiovascular magnetic resonance (CMR) imaging parameters for the assessment of the occurrence of major adverse cardiac events, displayed by chi-square values on the y-axis. GCS = global circumferential strain; GLS = left ventricular global longitudinal strain; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; MVO = microvascular obstruction.

Table 4
The occurrence of MACE in patients according to the median GCS and GLS and the randomization status

	GCS ≥−13.1%		GCS <−13.1%	
	Control (N = 65)	Metoprolol (N = 42)	Control (N = 45)	Metoprolol (N = 63)
MACE*	14 (21.5%)	4 (9.5%)	4 (8.9%)	3 (4.8%)
Death	3 (4.6%)	1 (2.4%)	1 (2.2%)	2 (3.2%)
Cardiac death	3 (4.6%)	0	0	0
Noncardiac death†	0	1 (2.4%)	1 (2.2%)	2 (3.2%)
HF admission	9 (13.8%)	3 (7.1%)	1 (2.2%)	1 (1.6%)
Reinfarction	3 (4.6%)	0	2 (4.4%)	0
	GLS ≥−11.5%		GLS <−11.5%	
	Control (N = 58)	Metoprolol (N = 49)	Control (N = 52)	Metoprolol (N = 56)
MACE*	15 (25.9%)	5 (10.2%)	3 (5.8%)	2 (3.6%)
Death	3 (5.2%)	1 (2.0%)	1 (1.9%)	2 (3.6%)
Cardiac death	3 (5.2%)	0	0	0
Non-cardiac death†	0	1 (2.0%)	1 (1.9%)	2 (3.6%)
HF admission	10 (17.2%)	4 (8.2%)	0	0
Re-infarction	3 (5.2%)	0	2 (3.8%)	0

GCS = global circumferential strain; GLS = global longitudinal strain; HF = heart failure; MACE = major adverse cardiac event.
* One patient in the impaired GCS/GLS group treated with conventional therapy experienced 2 events, however in MACE only the first event was included.
† All 4 noncardiac deaths were due to cancer.

in 247 STEMI and 451 STEMI patients, respectively. Similarly, our results show that both impaired LV GCS and GLS were strong predictors of adverse cardiac events after myocardial infarction and LV GLS analysis provided incremental prognostic value over conventional CMR parameters. Compared with the other studies, the patient population in our study was homogenous, consisting of anterior STEMI patients without signs of acute heart failure, prospectively included in the multicenter randomized controlled clinical trial.[7]

The different prognostic value of LV GLS and GCS might be the explained by the difference in LV mechanics described by both indices. During acute myocardial infarction myocardial cell injury spreads from the endocardium to the epicardium with increasing duration of coronary occlusion and severity of ischemia; the so-called "wavefront phenomenon of myocardial death."[19] Since the majority of longitudinally oriented myocardial fibers are located in the subendocardium[20] the LV longitudinal systolic function becomes impaired first. In contrast, the circumferential myocardial fibers that are found in the LV midwall[20] require a greater degree of transmural myocardial injury to impact on circumferential shortening. We may reasonably assume that impaired LV GCS reflects more severe myocardial injury and as such provides similar prognostic information to other CMR parameters. In contrast, the ability of LV GLS to account for the subendocardial infarct injury suggests that this parameter is a more sensitive marker of LV systolic dysfunction that adds additional prognostic information above other CMR parameters.

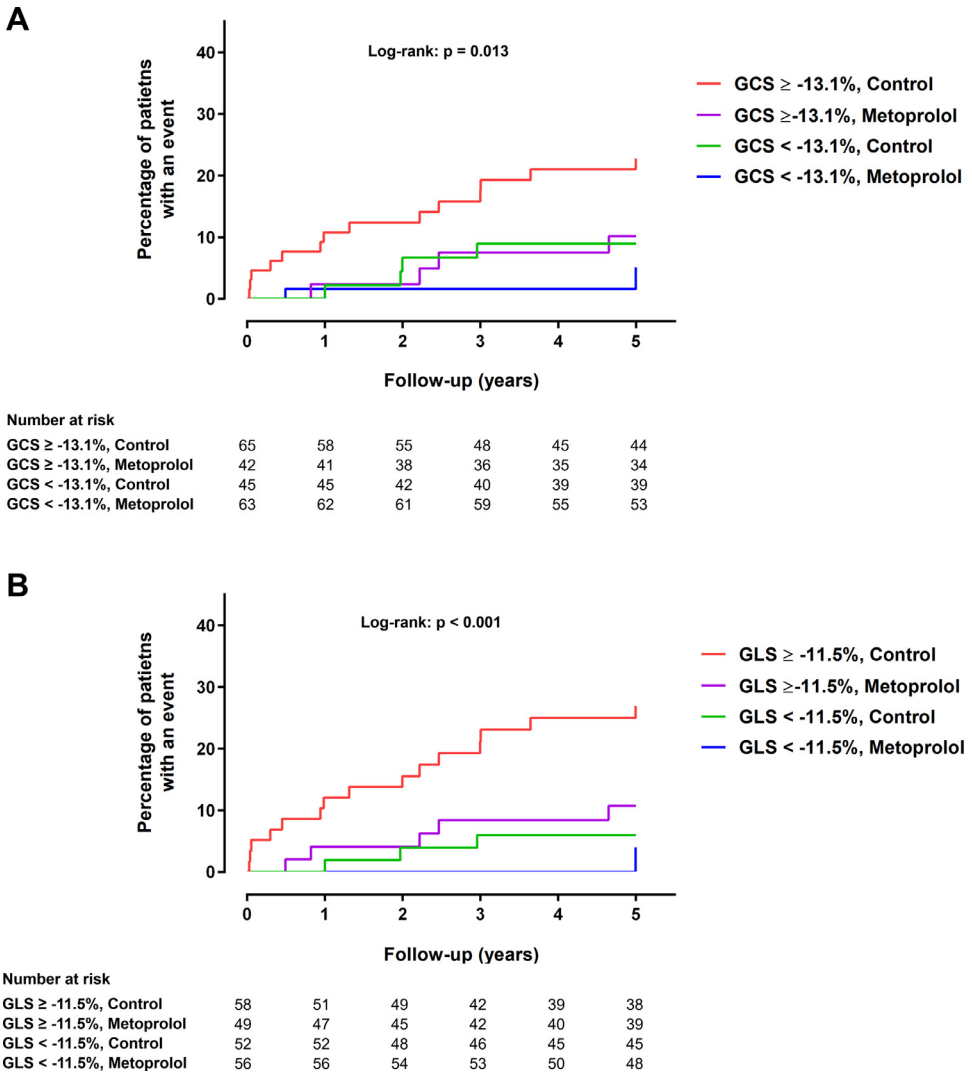

Figure 4. **Kaplan Meier estimates for cumulative major adverse cardiac event rates according to the global left ventricular strain and the randomization status.** ***(A)*** Patients were divided according to the global left ventricular circumferential strain (GCS) ≥−13.1% (more impaired) vs <−13.1% (more preserved) and the treatment group (early intravenous metoprolol vs control group). ***(B)*** Patients were divided according to the global left ventricular longitudinal strain (GLS) ≥−11.5% (more impaired) vs <−11.5% (more preserved) and the treatment group.

Feature-tracking is a novel technique to assess LV strain with CMR. Standardization of feature-tracking analysis as well as the reference values for LV strain and the agreement across various vendors of feature-tracking software are not established.[21] Furthermore, the evaluation of LV strain was not a predefined study endpoint of the METOCARD-CNIC trial. A limited number of events occurred during 5-year follow-up of patients included in the METOCARD clinical trial, which makes multivariable testing challenging, especially in the subgroup analysis. Of the initial 220 patients who underwent 1-week CMR study in the METOCARD-CNIC trial, 5 patients were excluded from the LV strain analysis due to poor CMR cine image quality (arrhythmias, metallic artifacts) which may have influenced our results. However, 98% feasibility of strain assessment with feature-tracking CMR is similar to what has been described before.[22,23] In addition, excellent intra- and interobserver reproducibility of feature-tracking analysis in our institution have been reported.[16]

In conclusion, early intravenous metoprolol has a long-term beneficial prognostic effect, particularly in patients who were at a greater risk for the occurrence of MACE due to severely impaired LV systolic function. Moreover, global LV strain assessment with feature-tracking CMR early after primary PCI provides important information in risk stratification of STEMI patients. LV GLS offers incremental prognostic value over traditional markers of LV injury, such as LVEF and infarct size with LGE.

Disclosures

Dr. Sánchez-González is a Philips Healthcare employee. Dr. Bucciarelli-Ducci is a consultant for Circle Cardiovascular Imaging. Dr. Ajmone Marsan and Dr. Bax received speaker fees from Abbott Vascular. Dr. Delgado received speaker fees from Abbott Vascular, Edwards Lifesciences, MSD, Medtronic and GE Healthcare. The remaining authors have nothing to disclose.

Author Contributions

Tomaz Podlesnikar: Conception and design of the study; collection, analysis and interpretation of data; statistical analysis; drafting of the manuscript; final approval of the manuscript

Gonzalo Pizarro: Conception and design of the study; collection, analysis and interpretation of data; statistical analysis; drafting of the manuscript; final approval of the manuscript

Rodrigo Fernández-Jiménez: Conception and design of the study; collection, analysis and interpretation of data; statistical analysis; drafting of the manuscript; final approval of the manuscript

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