



Universiteit
Leiden
The Netherlands

Multimodality imaging for myocardial injury in acute myocardial infarction and the assessment of valvular heart disease

Podlesnikar, T.

Citation

Podlesnikar, T. (2022, June 28). *Multimodality imaging for myocardial injury in acute myocardial infarction and the assessment of valvular heart disease*. Retrieved from <https://hdl.handle.net/1887/3420621>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/3420621>

Note: To cite this publication please use the final published version (if applicable).

4

Five-year outcomes and prognostic value of feature-tracking cardiovascular magnetic resonance in patients receiving early prereperfusion metoprolol in acute myocardial infarction

Tomaž Podlesnikar, Gonzalo Pizarro, Rodrigo Fernández-Jiménez, Jose M Montero-Cabezas, Javier Sánchez-González, Chiara Bucciarelli-Ducci, Nina Ajmone Marsan, Zlatko Fras, Jeroen J Bax, Valentin Fuster, Borja Ibáñez, Victoria Delgado

Am J Cardiol 2020;133:39-47

ABSTRACT

Background: 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.

Methods: 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 (PCI) 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 endpoint.

Results: Among 270 patients enrolled, 17 of 139 patients assigned to metoprolol arm and 31 of 131 patients assigned to control arm experienced MACE (HR:0.500, 95%CI:0.277-0.903; $P=0.022$). Impaired LV GCS and GLS strain were significantly associated with increased occurrence of MACE (GCS: HR:1.208, 95%CI:1.076-1.356, $P=0.001$; GLS: HR:1.362, 95%CI:1.180-1.573, $P<0.001$). 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 $\geq -11.5\%$ (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:0.129-0.979; $P=0.045$).

Conclusions: 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 PCI offers incremental prognostic value over conventional CMR parameters in risk stratification of STEMI patients.

INTRODUCTION

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 beta-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 three 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

Patient population

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 mmHg, PR interval >240 milliseconds (or type II-III atrioventricular block), heart rate persistently <60 bpm, or active treatment with any beta-blocker agent were excluded from the trial. All patients, including those in control arm, received oral metoprolol (first dose 12-24 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 character-

istics 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.

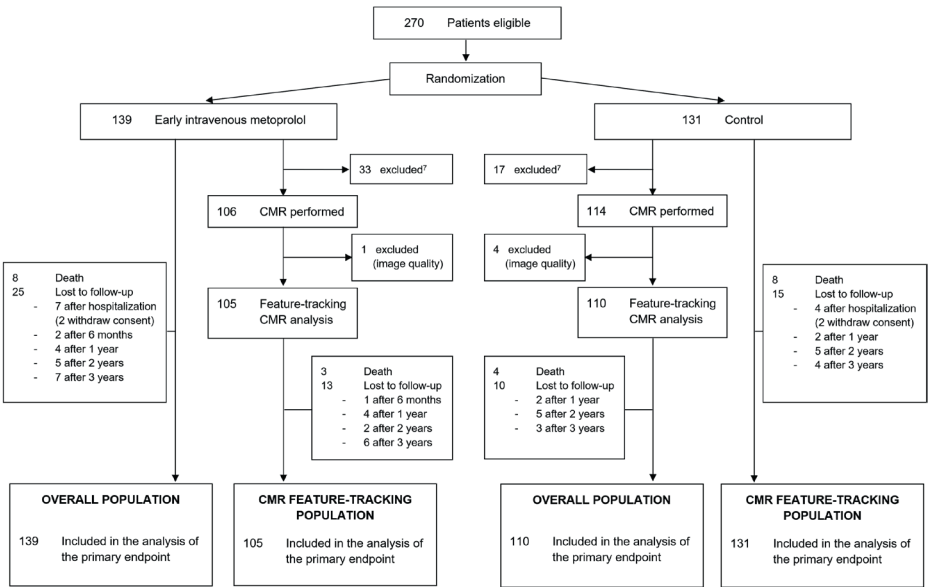


Figure 1: Study flow diagram. CMR = cardiovascular magnetic resonance.

Cardiovascular magnetic resonance data acquisition and conventional analysis

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 10-15 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 cardiovascular magnetic resonance analysis

Feature-tracking CMR analysis was performed with dedicated software (cvi⁴² 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.

Clinical endpoints

The primary endpoint 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 pre-specified METOCARD-CNIC trial endpoint.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-up⁸ 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, i.e. 1 week after STEMI, were included. In particular, all malignant ventricular arrhythmias occurred earlier and were not included in the analysis.

Statistical 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 endpoint 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 endpoint. 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 endpoint between individual groups. A two-sided P-value of <0.05 was statistically significant. All statistical analyses were performed using IBM SPSS Statistics 23 (IBM, Armonk, New York).

RESULTS

Impact of early intravenous metoprolol on long-term patient outcome

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: 0.277-0.903; P=0.022) and fewer heart failure admissions (HR 0.298, 95%CI: 0.096-0.924; P=0.036) (Table 1). The Kaplan-Meier curves for the occurrence of MACE in both treatment arms are shown in Figure 2.

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%)		
Non-cardiac death†	5 (3.6%)	2 (1.5%)		
HF admission	4 (2.9%)	12 (9.2%)	0.298 (0.096-0.924)	0.036
Re-infarction	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 non-cardiac deaths 6 were due to cancer and 1 due to hemoptysis (metoprolol group).

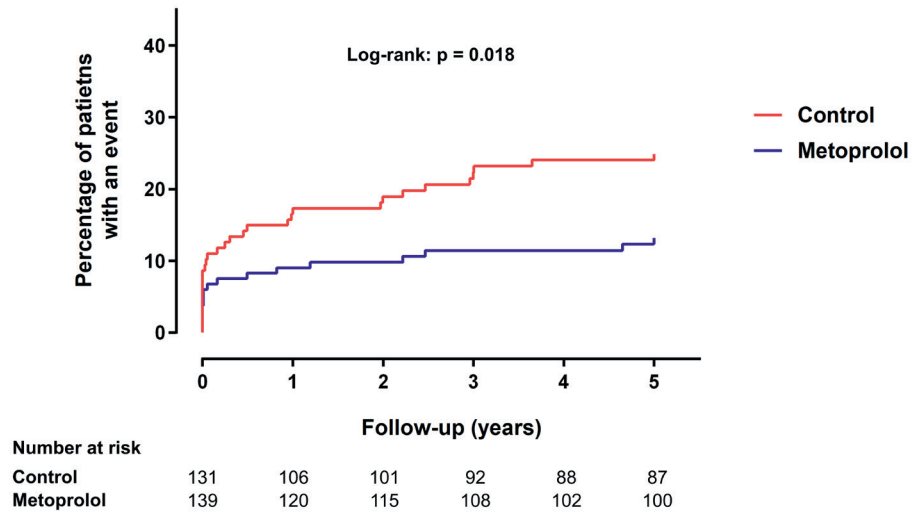


Figure 2: Kaplan Meier estimates for cumulative major adverse cardiac event rates in the overall METOCARD-CNIC trial population.

Prognostic value of LV GCS and GLS with feature-tracking CMR

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 to 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.

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

	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

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. Values are mean±SD, median (interquartile range) or n (%).
*Smoker was defined as current or quit <10 years ago.

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

	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 quit <10 years ago.

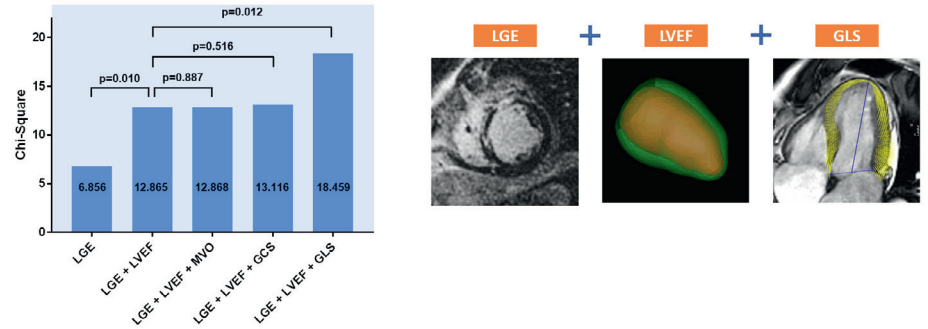


Figure 3: Incremental prognostic value of left ventricular strain with feature-tracking CMR. Bar graphs illustrate the prognostic value of cardiovascular magnetic resonance (CMR) imaging parameters for the assessment of the occurrence of major adverse cardiac events, displayed by chi-square values on 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.

Impact of early intravenous metoprolol on the prognostic value of LV GCS and GLS

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 ($\geq -11.5\%$) who received early intravenous metoprolol were 64% less likely to experience MACE (HR 0.356, 95%CI: 0.129-0.979; $P=0.045$) 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 ($\geq -13.1\%$) (HR for early metoprolol treatment 0.400, 95%CI: 0.132-1.216; $P=0.106$).

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

	GCS $\geq -13.1\%$		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
Non-cardiac 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%)
Re-infarction	3 (4.6%)	0	2 (4.4%)	0
	GLS $\geq -11.5\%$		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 non-cardiac deaths were due to cancer.

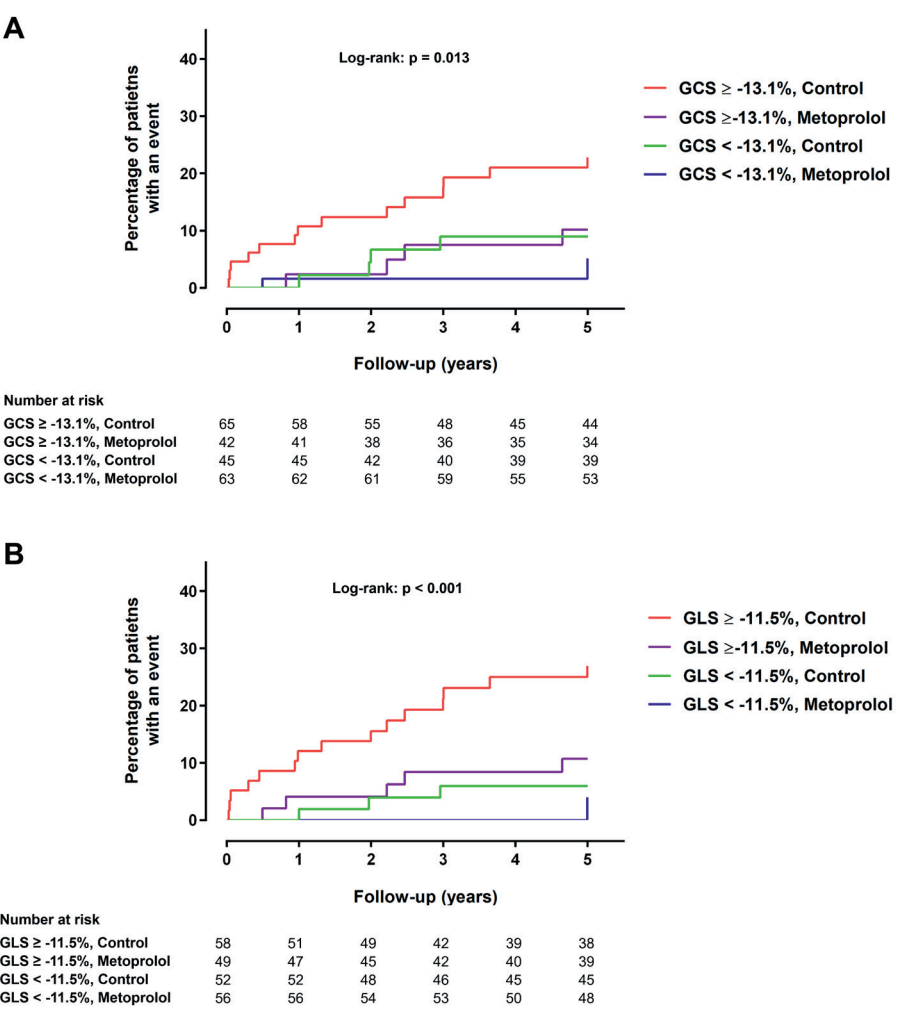


Figure 4: Kaplan Meier estimates for cumulative major adverse cardiac event rates according to the global left ventricular strain and the randomization status. (A) Patients were divided according to the global left ventricular circumferential strain (GCS) $\geq -13.1\%$ (more impaired) vs. $< -13.1\%$ (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) $\geq -11.5\%$ (more impaired) vs. $< -11.5\%$ (more preserved) and the treatment group.

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.

Long-term prognostic value of early intravenous metoprolol in STEMI

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 beta-blockers.⁷ Early intravenous administration of metoprolol (prior to primary PCI) was associated with significant reduction of primary endpoint, 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 towards reduced occurrence of pre-specified MACE (10.8% in the metoprolol group versus 18.3% in the control group; $P=0.065$) and a significant reduction in heart failure readmissions (2.2% in the metoprolol group versus 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 re-investigated with extended 5-year follow-up data and significant reduction in both, MACE as well as heart failure readmissions, was demonstrated. In addition, 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 beta-blockers.

Prognostic value of LV GCS and GLS with feature-tracking CMR

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 1107 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 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 to 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 multi-center randomized controlled clinical trial.⁷

Why LV GLS provides incremental prognostic value over conventional CMR parameters of myocardial damage after STEMI and LV GCS does not?

The different prognostic value of LV GLS and GCS might be 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 subendocardium²⁰ the LV longitudinal systolic function becomes impaired first. On the other hand, the circumferential myocardial fibers that are found in the LV midwall²⁰ 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. On the other hand, 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.

Study limitations

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 evalua-

tion 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 artefacts) 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 inter-observer reproducibility of feature-tracking analysis in our institution have been reported.¹⁶

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.

REFERENCES

1. Puymirat E, Simon T, Cayla G, Cottin Y, Elbaz M, Coste P *et al.* Acute Myocardial Infarction: Changes in Patient Characteristics, Management, and 6-Month Outcomes Over a Period of 20 Years in the FAST-MI Program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) 1995 to 2015. *Circulation* 2017;136(20):1908-19.
2. Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C *et al.* Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995-2014. *Eur Heart J* 2017;38(41):3056-65.
3. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H *et al.* 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(2):119-77.
4. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;61(4):485-510.
5. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. *N Engl J Med* 2007;357(11):1121-35.
6. Ibanez B, Heusch G, Ovize M, Van de Werf F. Evolving therapies for myocardial ischemia/reperfusion injury. *J Am Coll Cardiol* 2015;65(14):1454-71.
7. Ibanez B, Macaya C, Sanchez-Brunete V, Pizarro G, Fernandez-Friera L, Mateos A *et al.* Effect of early metoprolol on infarct size in ST-segment-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial. *Circulation* 2013;128(14):1495-503.
8. Pizarro G, Fernandez-Friera L, Fuster V, Fernandez-Jimenez R, Garcia-Ruiz JM, Garcia-Alvarez A *et al.* Long-term benefit of early pre-reperfusion metoprolol administration in patients with acute myocardial infarction: results from the METOCARD-CNIC trial (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction). *J Am Coll Cardiol* 2014;63(22):2356-62.
9. Eitel I, Stiermaier T, Lange T, Rommel KP, Koschalka A, Kowallick JT *et al.* Cardiac Magnetic Resonance Myocardial Feature Tracking for Optimized Prediction of Cardiovascular Events Following Myocardial Infarction. *JACC Cardiovasc Imaging* 2018;11(10):1433-44.

10. Gavara J, Rodriguez-Palomares JF, Valente F, Monmeneu JV, Lopez-Lereu MP, Bonanad C *et al.* Prognostic Value of Strain by Tissue Tracking Cardiac Magnetic Resonance After ST-Segment Elevation Myocardial Infarction. *JACC Cardiovasc Imaging* 2018;11(10):1448-57.
11. Yoon YE, Kang SH, Choi HM, Jeong S, Sung JM, Lee SE *et al.* Prediction of infarct size and adverse cardiac outcomes by tissue tracking-cardiac magnetic resonance imaging in ST-segment elevation myocardial infarction. *Eur Radiol* 2018;28(8):3454-63.
12. Reindl M, Tiller C, Holzknrecht M, Lechner I, Beck A, Plappert D *et al.* Prognostic Implications of Global Longitudinal Strain by Feature-Tracking Cardiac Magnetic Resonance in ST-Elevation Myocardial Infarction. *Circ Cardiovasc Imaging* 2019;12(11):e009404.
13. Mangion K, Carrick D, Clerfond G, Rush C, McComb C, Oldroyd KG *et al.* Predictors of segmental myocardial functional recovery in patients after an acute ST-Elevation myocardial infarction. *Eur J Radiol* 2019;112:121-9.
14. Nucifora G, Muser D, Tioni C, Shah R, Selvanayagam JB. Prognostic value of myocardial deformation imaging by cardiac magnetic resonance feature-tracking in patients with a first ST-segment elevation myocardial infarction. *Int J Cardiol* 2018;271:387-91.
15. Ibanez B, Fuster V, Macaya C, Sanchez-Brunete V, Pizarro G, Lopez-Romero P *et al.* Study design for the “effect of METOpriolol in CARDioprotection during an acute myocardial Infarction” (METOCARD-CNIC): a randomized, controlled parallel-group, observer-blinded clinical trial of early pre-reperfusion metoprolol administration in ST-segment elevation myocardial infarction. *Am Heart J* 2012;164(4):473-80.e5.
16. Podlesnikar T, Pizarro G, Fernandez-Jimenez R, Montero-Cabezas JM, Sanchez-Gonzalez J, Buccioni-Ducci C *et al.* Effect of Early Metoprolol During ST-Segment Elevation Myocardial Infarction on Left Ventricular Strain: Feature-Tracking Cardiovascular Magnetic Resonance Substudy From the METOCARD-CNIC Trial. *JACC Cardiovasc Imaging* 2019;12(7 Pt 1):1188-98.
17. Podlesnikar T, Pizarro G, Fernández-Jiménez R, Montero-Cabezas JM, Greif N, Sánchez-González J *et al.* Left ventricular functional recovery of infarcted and remote myocardium after ST-segment elevation myocardial infarction (METOCARD-CNIC randomized clinical trial substudy). *J Cardiovasc Magn Reson* 2020;22(1):44.
18. Mangion K, McComb C, Auger DA, Epstein FH, Berry C. Magnetic Resonance Imaging of Myocardial Strain After Acute ST-Segment-Elevation Myocardial Infarction: A Systematic Review. *Circ Cardiovasc Imaging* 2017;10(8).
19. 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(5):786-94.

20. Greenbaum RA, Ho SY, Gibson DG, Becker AE, Anderson RH. Left ventricular fibre architecture in man. *Br Heart J* 1981;45(3):248-63.
21. Amzulescu MS, De Craene M, Langet H, Pasquet A, Vancraeynest D, Pouleur AC *et al.* Myocardial strain imaging: review of general principles, validation, and sources of discrepancies. *European heart journal cardiovascular Imaging* 2019;20(6):605-19.
22. Augustine D, Lewandowski AJ, Lazdam M, Rai A, Francis J, Myerson S *et al.* Global and regional left ventricular myocardial deformation measures by magnetic resonance feature tracking in healthy volunteers: comparison with tagging and relevance of gender. *J Cardiovasc Magn Reson* 2013;15:8.
23. Andre F, Steen H, Matheis P, Westkott M, Breuninger K, Sander Y *et al.* Age- and gender-related normal left ventricular deformation assessed by cardiovascular magnetic resonance feature tracking. *J Cardiovasc Magn Reson* 2015;17:25.