Int J Cardiovasc Imaging (2013) 29:1499–1509
DOI 10.1007/s10554-013-0239-1

ORIGINAL PAPER

Head-to-head comparison of 1 week versus 6 months CMR-derived infarct size for prediction of late events after STEMI

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Received: 12 February 2013 / Accepted: 15 May 2013 / Published online: 4 June 2013

Abstract Infarct size (IS) at 1 week after ST-elevation myocardial infarction (MI) diminishes during the first months. The incremental prognostic value of IS regression and of scar size (SS) at 6 months is unknown. We compared cardiovascular magnetic resonance (CMR)-derived IS at 1 week and SS at 6 months after MI for predicting late major adverse cardiac events (MACE). 250 patients underwent CMR at 1 week and 6 months after MI. IS and SS were determined as the extent of transmural late enhancement (in >50 % of wall thickness, ETLE). During 163 weeks, 23 late MACE (cardiac death, MI or readmission for heart failure after the 6 months CMR) occurred. Patients with MACE had a larger IS at 1 week (6 [4–9] vs. 3 [1–5], $p < .0001$) and a larger SS at 6 months (5 [2–6] vs. 3 [1–5], $p = .005$) than those without MACE. Late MACE rates in IS >median were higher at 1 week (14 vs. 4 %, $p = .007$) and in SS >median at 6 months (12 vs. 5 %, $p = .053$). The C-statistic for predicting late MACE of CMR at 1 week and 6 months was comparable (.720 vs. .746, $p = .1$). Only ETLE at 1 week (HR 1.31 95 % CI [1.14–1.52], $p < .0001$, per segment) independently predicted late MACE. CMR-derived SS at 6 months does not offer prognostic value beyond IS at 1 week after MI. The strongest predictor of late MACE is ETLE at 1 week.

Keywords Cardiovascular magnetic resonance · ST-elevation myocardial infarction · Prognosis · Late gadolinium enhancement imaging

Electronic supplementary material The online version of this article (doi:10.1007/s10554-013-0239-1) contains supplementary material, which is available to authorized users.

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Introduction

Cardiovascular magnetic resonance imaging (CMR) allows for a state of the art assessment of patients after ST-elevation myocardial infarction (STEMI) [1, 2]. CMR has shown a unique value for assessing infarct size based on late gadolinium enhancement imaging (LGE) [3]. Both a quantitative assessment of infarct size (expressed as percentage of the left ventricle (LV)) as well as a semiquantitative assessment of the number of segments showing transmural necrosis (in >50 % of their wall thickness) have been used to predict late systolic recovery and outcome after STEMI [4]. The prognostic value of a CMR examination, carried out in the post-acute phase (around 1 week) after STEMI has been established [5–7]. Among different myocardial infarction parameters, especially

infarct size has been identified as a predictor of adverse outcome and adverse LV remodelling [5, 7–9].

Several studies, using repeated CMR examinations for the longitudinal assessment of the evolution of myocardial infarct parameters and cardiac remodelling, have been mostly carried out within the time frame of 4–6 months after STEMI and were not focused on outcome. These studies have demonstrated a marked regression of scar size [7, 10–12]. Over time, of the initial infarct size, reabsorption of myocardial edema, replacement of myofibroblasts and scar contraction lead to a remaining final scar size [13, 14]. However, the prognostic implications of these processes and of the final scar size after STEMI in a follow-up CMR study beyond the information obtained in the post-acute phase have not been analyzed. Moreover, whether or not, a routine repeated CMR study in the late phase after STEMI is warranted for prognostic purposes is of increasing importance in times of economic shortage.

We hypothesized that a repeated late CMR study after STEMI may offer additional prognostic value beyond the information obtained in the post-acute phase. Therefore we performed a head-to-head comparison of the prognostic value of infarct size derived from a 1 week CMR study versus scar size at a 6 months CMR study after STEMI in terms of late major adverse cardiac events (MACE) during long-term follow-up.

Methods

Study group and reperfusion therapy

This is an ongoing prospective registry including consecutive patients undergoing CMR after a first STEMI [4, 5]. In the present study, 335 consecutive patients, admitted to our institution with a first STEMI from November 2006 to December 2010, were evaluated for eligibility. Patients with a previous myocardial infarction were not considered for participation. Previous coronary artery disease (documented on angiography with or without previous percutaneous intervention or history of angina unrelated to the current event) was not an exclusion criterion. Of these patients, 289 underwent CMR at 1 week after STEMI. CMR was repeated at 6 months in 250 patients, constituting the study population. CMR was not repeated in 39 cases, because of death (n = 3), contraindications to CMR (n = 22) or due to patient's or cardiologist's decision (n = 22) (see Fig. 1). Our institutional ethics committee approved the study protocol and written informed consent was obtained from all subjects. The study was conducted in accordance with the Declaration of Helsinki.

All baseline clinical characteristics, ECG data and laboratory parameters were determined prospectively on patient admission and after reperfusion.

Reperfusion strategy and medical treatment were left to the discretion of the attending cardiologists. There were 30 patients (12 %) who did not receive reperfusion therapy within the first 12 h after symptom onset due to delayed presentation. Coronary angiography and, if necessary, angioplasty was performed in these patients during hospitalization. Primary percutaneous coronary intervention (PCI) was performed in 85 patients (34 %). A pharmaco-invasive strategy, consisting of thrombolysis with routine angiography and, if required, angioplasty, was employed in 137 patients (54 %). Of patients receiving thrombolytics, 31 patients required rescue angioplasty.

Thrombolysis in myocardial infarction (TIMI) flow grade and myocardial blush grade in the final angiography of the infarct related artery were determined offline by an experienced observer using standard software (Integris HM3000, Philips, Best, the Netherlands). TIMI flow grade 3 and myocardial blush grade 2–3 were regarded as normal [15].

CMR study

CMR (1.5-T, Sonata Magnetom, Siemens, Erlangen, Germany) was performed according to our laboratory protocol [4, 16]. All images were acquired by a phased-array body surface coil during breath-holds and were ECG-triggered.

Cine images were acquired at rest in 2-, 3-, 4-chamber views and every 1 cm in short-axis views using steady-state free precession imaging sequences (repetition time/echo time: 3.2/1.6 ms, flip angle: 61°, matrix: 256 × 128, slice thickness: 6 mm, temporal resolution: 26 ms).

Black blood, T2-weighted STIR (short TI inversion recovery) sequences in the same short-axis view as the cine sequences, all in mid-diastole were carried out. A half-Fourier acquisition single-shot turbo spin echo (HASTE) multisection sequence was used (TR, 2 R–R intervals; TE, 33 ms; TI, 170 ms; slice thickness, 8 mm; interslice interval, 2 mm; flip angle, 160°; matrix, 256 × 151; bandwidth, 781 Hz/pixel) [17]. Additionally, a segmented turbo-spin echo (TSE) sequence was obtained with 1 slice per breath-hold (TR, 2 R–R intervals; TE, 100 ms; TI, 170 ms; slice thickness, 8 mm; interval, 2 mm; flip angle, 180°; matrix, 256 × 146; bandwidth, 235 Hz/pixel) [18, 19].

Late gadolinium enhancement (LGE) imaging was performed in the same projections used for cine images at least 10 min after administering .1 mmol/kg of gadopentetate dimeglumine; Magnevist®. A segmented inversion recovery steady-state free precession imaging sequence was used (repetition time/echo time: 750/1.26 ms, flip angle: 45°, matrix: 256 × 184, field of view: 340 × 235 mm, slice thickness: 7 mm) nullifying myocardial signal.

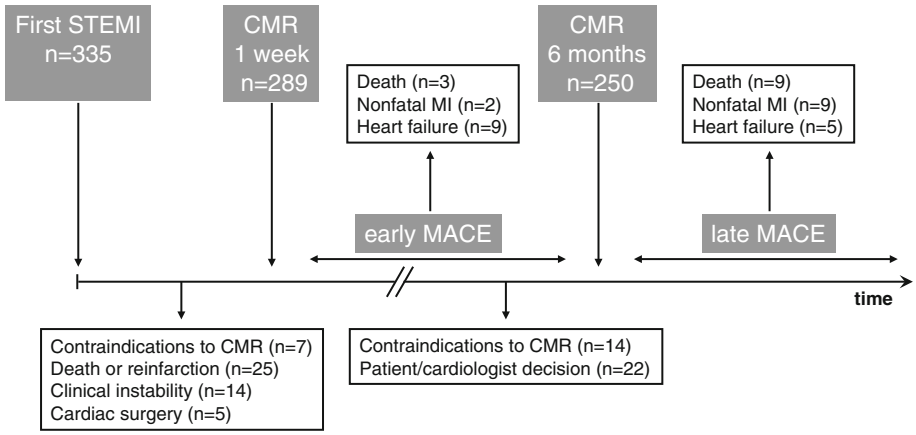


Fig. 1 Patient flow chart and study design. Reasons for exclusion of patients from the study and occurrence of early and late MACE. *CMR* cardiovascular magnetic resonance, *MACE* major adverse cardiac events, *STEMI* ST elevation myocardial infarction, *MI* myocardial infarction

CMR data analysis

CMR studies were analyzed by an experienced observer blinded to all patient data using customized software (QMASS MR, 6.1.5, Medis, Leiden, The Netherlands).

LV ejection fraction (%), end-diastolic and end-systolic volume indexes (ml/m^2) and mass (g/m^2) were calculated by manual planimetry of endocardial and epicardial borders in all short-axis views cine images.

For the evaluation of myocardial area at risk/edema, TSE sequences were used in 205 patients (82 %) due to the superior quality. Since this sequence is prone to motion artifacts, in the remaining cases, myocardial edema was evaluated using HASTE sequences. Myocardial edema was automatically quantified as areas of high T2 signal intensity (>2 standard deviations greater with respect to remote non-infarcted myocardium) and manually corrected by an expert observer. Myocardial edema was expressed as percentage of LV mass. The finding of a low-signal-intensity area surrounded by a high-signal-intensity area (i.e. edema) in these images was considered to indicate an area of intramyocardial hemorrhage.

T2 sequences were repeated at 6 months. Since edema was absent in the first 70 patients, the acquisition of T2 sequences at 6 months was abandoned and myocardial edema was only evaluated in the 1 week CMR study.

LGE was considered present if signal intensity was >2 standard deviations with respect to a remote non-infarcted area in LGE imaging (Fig. 2) [20]. Areas showing LGE were automatically detected. All cases were manually revised and corrected if necessary.

CMR derived-infarct size at both time points was assessed using 2 definitions: (1) the percentage of LV mass showing LGE (IS%LV) and (2) the extent of transmural (in more than 50 % of wall thickness) late enhancement (ETLE) according to the 17 segment model [21].

Microvascular obstruction (MVO) was visually defined on a segmental basis as a lack of contrast uptake in the core of a segment surrounded by tissue showing LGE [22]. The number of segments displaying MVO was determined.

Salvaged myocardium was defined as the difference between the area at risk and the area of necrosis, expressed as the percent of LV mass or percent area at risk.

For the determination of the intraobserver variability of the ETLE and MVO the same operators quantified the CMR indexes at two different time points in 100 randomly selected patients. The intraobserver variability for the determination these CMR parameters in our group is less than 5 % [4, 23].

Endpoints and follow-up

The endpoint of the study was late MACE defined as a composite of cardiac death, admission for nonfatal myocardial infarction [24] or for heart failure [25] whichever occurred first after the 6 months CMR. Patients who experienced a nonfatal myocardial infarction or readmission for heart failure before the 6 months CMR study were not censored for the analysis of late MACE. Follow-up was centrally updated every 3 months by 2 cardiologists and 2 trained nurses from at least one of 3 sources: (1) the outpatients' clinic; (2) a telephone interview with the patient or his/her family conducted by a cardiologist or (3) review of the patient's hospital record. An independent adjudication process, including review of clinical histories was applied and consensus between two cardiologists was required to finally adjudicate an event.

Statistical analysis

All data were tested for normal distribution using the one-sample Kolmogorov–Smirnov test. Continuous normally distributed data were expressed as the mean ± standard deviation and compared using the paired or unpaired Student's *t* test where appropriate. Non-parametric data (expressed as the median with the interquartile range) were compared with the Mann–Whitney U test or the Wilcoxon

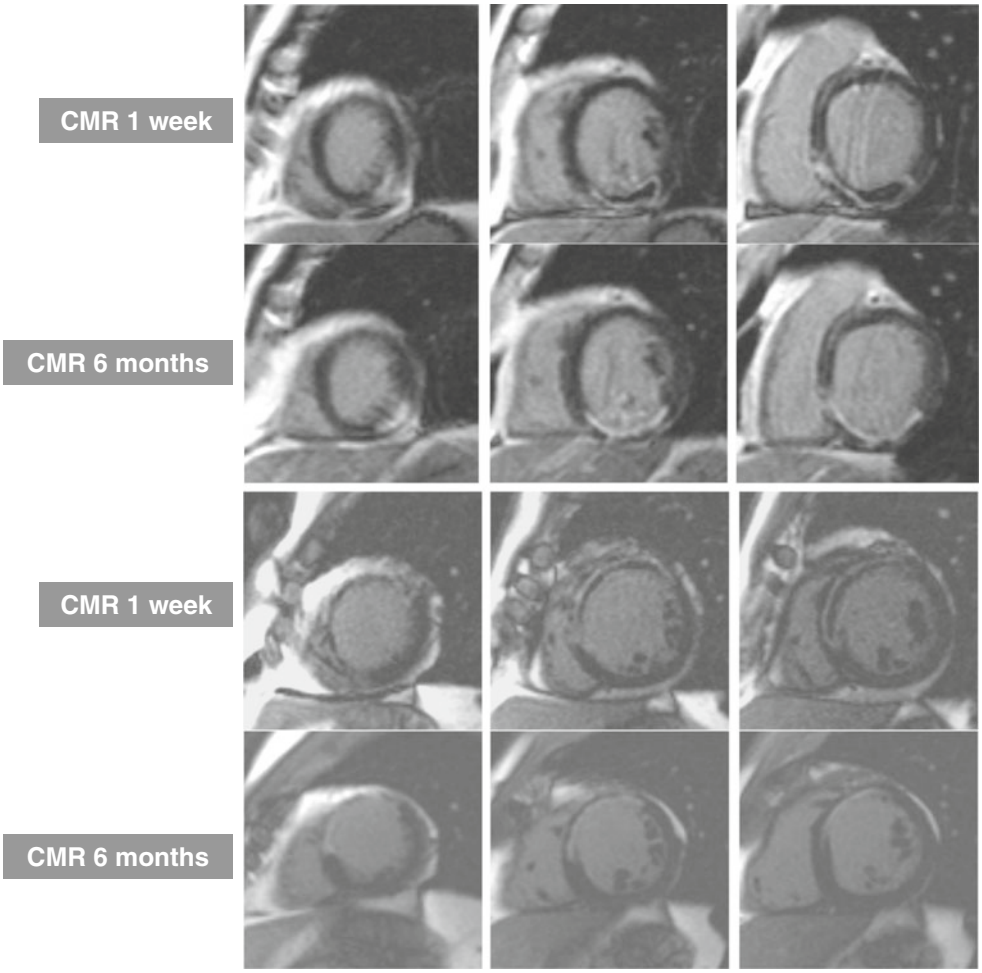


Fig. 2 Example of CMR studies at 1 week and 6 months. The figure shows the CMR studies of 2 patients. The *upper row* shows the 1st week late gadolinium enhancement CMR study. The *lower rows* show the CMR study at the 6th month of the same patients. Infarct size has diminished and microvascular obstruction has disappeared. *CMR* cardiovascular magnetic resonance

Signed Ranks test where appropriate. Group percentages were compared using the Chi square test or Fisher's exact test.

For dichotomic univariate analysis, we implemented cut-off values on the basis of the area under the receiver operating characteristics curves (AUCs) of the two infarct size indexes (IS%LV and ETLE) for predicting late MACE by maximizing the observed overall diagnostic accuracy (minimizing the number of false positives plus the number of false negatives). The resulting cut-off values were: IS%LV 1 week $>$ 27.7 %; 6 months $>$ 30.9 % ETLE 1 week $>$ 4 segments; 6 months $>$ 4 segments.

Survival distributions for the time to event were estimated with the Kaplan–Meier method and the log-rank test.

The association of CMR-derived infarct size indexes at both 1 week and 6 months with the time to late MACE was assessed using a Cox proportional hazard regression model with stepwise forward multivariate procedures adjusted for all baseline, angiographic and CMR characteristics significantly associated with late MACE in univariate analyses ($p < .05$). Hazard ratios (HR) with the corresponding 95 % confidence intervals (CI) were computed.

The individual capacity of CMR-derived infarct size indexes at 1 week and at 6 months for predicting late MACE was assessed by calculating the C-statistic derived from the respective Cox proportional hazard regression models. The AUCs were compared.

Statistical significance was considered for two-tailed p value $<.05$. SPSS 13.0 (SPSS Inc, Chicago, Illinois, USA) and STATA 11.0 (StataCorp, College Station, Texas, USA) were used.

Results

Study population and baseline characteristics

The median follow-up was 163 weeks [67–237]. In the early phase after STEMI (1 week–6 months), 14 early

MACE (3 cardiac deaths, 2 myocardial infarctions and 9 admissions for heart failure) occurred, while there were 23 late MACE (9 cardiac deaths, 9 nonfatal myocardial infarctions and 5 readmissions for heart failure, see Fig. 1).

The baseline characteristics of the entire patient population and according to the occurrence of late MACE are displayed in Table 1. Patients with late MACE had a higher prevalence of previous coronary artery disease (17 vs. 3 %, $p = .001$) and a higher median peak creatine kinase MB (333 [178–500] ng/ml vs. 195 [84–307], $p = .007$) with a significantly higher rate of anterior infarctions (83 vs. 53 %, $p = .006$). Myocardial blush grade 2–3 after PCI was observed with a significantly lower rate in patients with late MACE (57 vs. 78 %, $p = .02$).

CMR at 1 week and 6 months

The temporal evolution of the CMR indexes from 1 week to 6 months is displayed in Table 2. There was a significant improvement of LV ejection fraction (52 ± 13 % vs. 55 ± 14 %, Δ 3 % [−3–9], $p < .001$) and regression of LV mass (72 ± 17 g/m^2 vs. 66 ± 17, Δ −6 [−13–1], $p < .001$).

CMR-derived infarct size, expressed as IS%LV as well as ETLE significantly decreased (see Fig. 3). In contrast, LV volumes did not change significantly, albeit there was a non-significant trend towards smaller LV end-systolic volumes at 6 months ($p = .07$).

CMR characteristics according to late MACE

The CMR characteristics at 1 week and 6 months according to the occurrence of late MACE are presented in Table 3. At both time points, patients with late MACE showed significantly lower LV ejection fractions (%) (1 week: 43 ± 13 vs. 53 ± 12, $p < .001$, 6 months: 45 ± 16 vs. 56 ± 14, $p < .001$). CMR-derived infarct size was larger in patients with late MACE compared to those without late MACE (IS%LV, 1 week: 32 ± 17 vs. 21 ± 14, $p = .001$; 6 month: 28 ± 15 vs. 17 ± 13, $p < .001$ and ETLE (number of segments), 1 week: 6 [4–9] vs. 3 [1–5], $p < .0001$; 6 months: 5 [2–6] vs. 3 [1–5], $p = .005$). LV volumes and masses as well as the number of segments with MVO did not differ significantly between both groups at either time point. The changes in CMR indexes (expressed as the Δ) did not show any significant difference between both groups (Table 3). The association of CMR parameters at 1 week with the occurrence of early MACE (including the 3 deaths) is displayed in the supplementary table. The association of the presence of

Table 1 Clinical and angiographic characteristics of the entire patient population and according to the occurrence of late major adverse cardiac events

	All patients (n = 250)	Late MACE (n = 23)	No late MACE (n = 227)	*p* value
Age (years)	58 ± 12	59 ± 13	58 ± 12	.8
Male sex (%)	206 (83)	21 (91)	185 (82)	.2
Diabetes (%)	40 (16)	2 (9)	38 (17)	.3
Hypertension (%)	111 (45)	10 (44)	101 (45)	.9
Hypercholesterolemia (%)	94 (38)	9 (39)	85 (37)	.9
Previous coronary artery disease (%)	11 (4)	4 (17)	7 (3)	.001
Smoker (%)	153 (61)	16 (70)	136 (60)	.4
Heart rate (beats per minute)	81 ± 20	93 ± 28	80 ± 19	.03
Systolic blood pressure (mmHg)	127 ± 27	125 ± 29	127 ± 26	.7
Killip class >1	26 (10)	1 (5)	25 (11)	.4
Primary angioplasty within 12 h (%)	84 (34)	6 (26)	78 (34)	.4
Thrombolysis within 12 h (%)	136 (54)	16 (70)	120 (53)	.1
Rescue angioplasty (%)	31 (12)	4 (17)	27 (12)	.5
Reperfusion within 12 h (%)	220 (88)	22 (96)	198 (87)	.2
Time to reperfusion (min)	246 ± 172	269 ± 188	243 ± 170	.5
Median ST-segment resolution (%)	84 [63–100]	71 [50–86]	85 [64–100]	.05
Median peak creatine kinase-MB (ng/ml)	199 [88–337]	333 [178–500]	195 [84–307]	.007
Proximal left anterior descending lesion (%)	69 (27)	10 (44)	59 (26)	.07
Anterior infarction (%)	139 (56)	19 (83)	120 (53)	.006
Final myocardial blush grade 2–3 (%)	190 (76)	13 (57)	177 (78)	.02
Final TIMI 3 in IRA (%)	231 (92)	23 (100)	208 (92)	.2

MACE major adverse cardiac event, *TIMI* thrombolysis in myocardial infarction, *PCI* percutaneous coronary intervention, *IRA* infarct related artery

Table 2 Evolution CMR indexes from 1 week to 6 months (n = 250)

	1st week	6th month	Δ	*p* value
LV ejection fraction (%)	52 ± 13	55 ± 14	3 [−3–9]	<.001
LV end-diastolic volume (ml/m^2)	80 ± 24	79 ± 25	−1 [−11–12]	.7
LV end-systolic volume (ml/m^2)	39 ± 21	38 ± 23	−3 [−8–5]	.07
LV mass (g/m^2)	72 ± 17	66 ± 17	−6 [−13–1]	<.001
Area at risk/edema (% of LV mass)	30 ± 16	nd	–	–
Myocardial salvage (% of LV mass)	5 [1–12]	nd	–	–
No. of segments with IMH	0 [0–2]	nd	–	–
No. of segments with MVO	0 [0–2]	0 [0–0]	0 [−2–0]	<.001
ETLE (no. of segments)	4 [2–5]	3 [1–5]	0 [−1–0]	<.001
IS%LV	22 ± 15	18 ± 13	−3 [−7–1]	<.001

CMR cardiovascular magnetic resonance, *LV* left ventricular, *nd* not determined, *ETLE* no. of segments with transmural (in more than 50 % of wall thickness) late gadolinium enhancement, *IS%LV* infarct size expressed as a percentage of LV, *IMH* intramyocardial haemorrhage, *MVO* microvascular obstruction

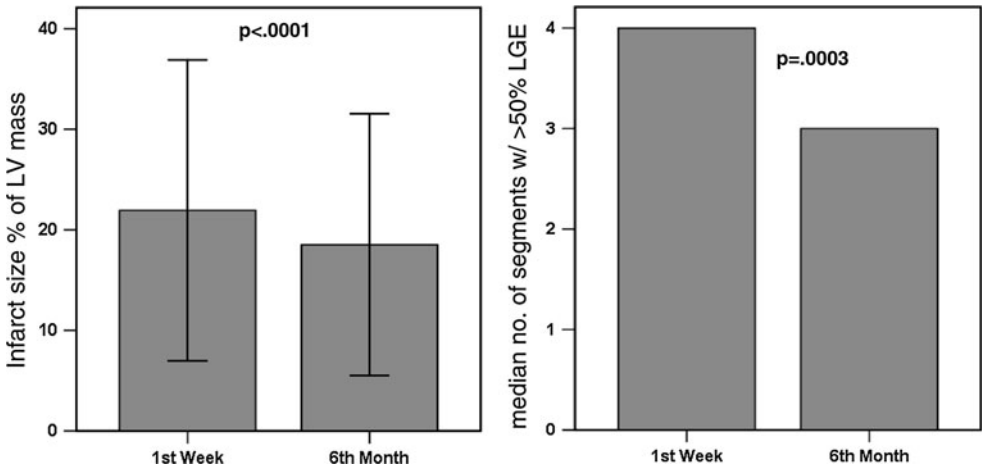


Fig. 3 Evolution of infarct size from 1 week to 6 months. Regression of infarct size from 1 week to 6 months. *Left panel* shows a significant reduction of mean infarct size (% of left ventricular (LV) mass, 22 ± 15 % vs. 18 ± 13, $p < .0001$, Δ −3 [−7–1]). Right panel shows the median number of segments with transmural necrosis (>50 % late gadolinium enhancement) at both time points (4 [2–5 vs. 3 [1–5], $p = .0003$ Δ 0 [−1–0])

MVO (0–1 vs. 2 + segments) with early and late MACE is displayed in the supplementary figure 1.

Infarct size at 1 week versus 6 months and occurrence of late MACE

In order to determine the optimal cut-off of infarct size indexes for discriminating the risk of late MACE, the patient population was categorized according to cut-off values established on the basis of the AUCs of the two infarct size indexes for predicting late MACE at 1 week and 6 months. The crude late MACE rate in these groups was: IS%LV (>27.7 % 1 week: 21 vs. 4 %, $p < .0001$; >30.9 % 6 months: 17 vs. 5 %, $p = .003$), ETLE (>4 segments 1 week: 18 vs. 5 %, $p = .002$; >4 segments 6 months: 26 vs. 5 %, $p < .0001$). The Kaplan–Meier curves for survival free of late MACE according to these cut-offs for ETLE are depicted in Fig. 4. The AUCs of both CMR-derived infarct indexes for the prediction of late MACE are displayed in Fig. 5. Both indexes at both time points displayed a comparable AUC for predicting late MACE, albeit there was a non-significant trend towards a larger AUC with ETLE at 1 week compared to 6 month (.759 [.701–.811] vs. .678 [.616–.736], $p = .1$).

CMR predictors of late MACE at 1 week and 6 months

The AUC of the model containing all CMR variables at 1 week yielding a *p* value of <.05 in the univariate analysis was comparable to the model containing 6 months CMR variables (.720 [.660–.774] vs. .746 [.687–.798], $p = .1$, Fig. 6). Cox proportional hazard regression models adjusted for baseline clinical and angiographic variables were performed (see Table 4). The first model included only CMR variables available at 1 week. The only independent CMR predictor of late MACE was the ETLE (HR 1.313 95 % CI [1.135–1.519], $p < .0001$, per segment). Previous coronary artery disease was the only baseline variable associated with late MACE (HR 13.893 95 % CI [3.991–48.361], $p < .0001$). The addition of CMR

Table 3 CMR characteristics at 1 week and 6 months according to late major adverse cardiac events

	Late MACE (n = 23)	No late MACE (n = 227)	*p* value
CMR 1 week			
LV ejection fraction (%)	43 ± 13	53 ± 12	<.001
LV end-diastolic volume (ml/m^2)	75 ± 25	80 ± 23	.3
LV end-systolic volume (ml/m^2)	44 ± 23	39 ± 20	.3
LV mass (g/m^2)	74 ± 20	71 ± 16	.4
Area at risk/edema (% of LV mass)	38 ± 16	29 ± 15	.005
Myocardial salvage (% of LV mass)	6 [1–12]	4 [1–9]	.4
No. of segments with IMH	1 [0–3]	0 [0–2]	.4
No. of segments with MVO	0 [0–3]	0 [0–2]	.7
ETLE (number of segments)	6 [4–9]	3 [1–5]	<.0001
IS%LV	32 ± 17	21 ± 14	.001
CMR 6 months			
LV ejection fraction (%)	45 ± 16	56 ± 14	<.001
LV end-diastolic volume (ml/m^2)	79 ± 33	79 ± 25	.9
LV end-systolic volume (ml/m^2)	47 ± 29	37 ± 22	.1
LV mass (g/m^2)	71 ± 22	66 ± 16	.2
No. of segments with microvascular obstruction	0 [0–0]	0 [0–0]	.5
ETLE (number of segments)	5 [2–6]	3 [1–5]	.005
IS%LV	28 ± 15	17 ± 13	<.001
Δ LV ejection fraction (%)	0 [−4–10]	3 [−3–8]	.7
Δ LV end-diastolic volume (ml/m^2)	2 [−8–13]	−2 [−12–11]	.2
Δ LV end-systolic volume (ml/m^2)	0 [−5–12]	−3 [−9–5]	.1
Δ LV mass (g/m^2)	−3 [−7–1]	−6 [−13–1]	.3
Δ No. of segments with microvascular obstruction	0 [−3–0]	0 [−2–0]	.9
Δ ETLE (number of segments)	0 [−3–0]	0 [−1–0]	.1
Δ IS%LV	−4 [−10–4]	−3 [−7–1]	.9

CMR cardiovascular magnetic resonance, *MACE* major adverse cardiac event, *LV* left ventricular, *ETLE* no. of segments with transmural (in more than 50 % of wall thickness) late gadolinium enhancement, *IS%LV* infarct size expressed as a percentage of LV, *IMH* intramyocardial haemorrhage, *MVO* microvascular obstruction

variables from 6 months to this model did not alter the results of the first model, leaving the ETLE at 1 week as the only independent CMR predictor of late MACE (HR 1.313 95 % CI [1.135–1.519], $p < .0001$).

Discussion

This study investigates whether the regression of CMR-derived infarct size during the first months after STEMI and the final scar size at 6 months offer prognostic value in terms of late MACE beyond information obtained in the post-acute phase at 1 week. We found that CMR-derived scar size (expressed as IS%LV and ETLE) at both time points was associated with late MACE (i.e. all MACE occurring from 6 months and onwards after STEMI). Nevertheless, the single strongest predictor among CMR-derived infarct size indexes was the ETLE at 1 week. No CMR variable at 6 months was retained in the multivariable model. Therefore, a repeated CMR study for assessing scar size at 6 months does not add to the predictive value of infarct size at 1 week for late MACE.

Serial CMR examinations after STEMI

Several studies, using serial LGE-CMR studies, have shown that final scar size is smaller than the initial infarct size in the acute phase after STEMI [7, 10]. This observation might occur due to initial overestimation of infarct size by peri-infarct edema [26] and inflammation or due to regeneration of cardiomyocytes by myofibroblasts [14, 27]. Also, the diminishing of scar size may also be the result of scar shrinking and contraction [13, 14] .

The potential to overestimate infarct size in the post-acute phase potentially warrants deferral or repetition of imaging at a later time point for prognostic purposes.

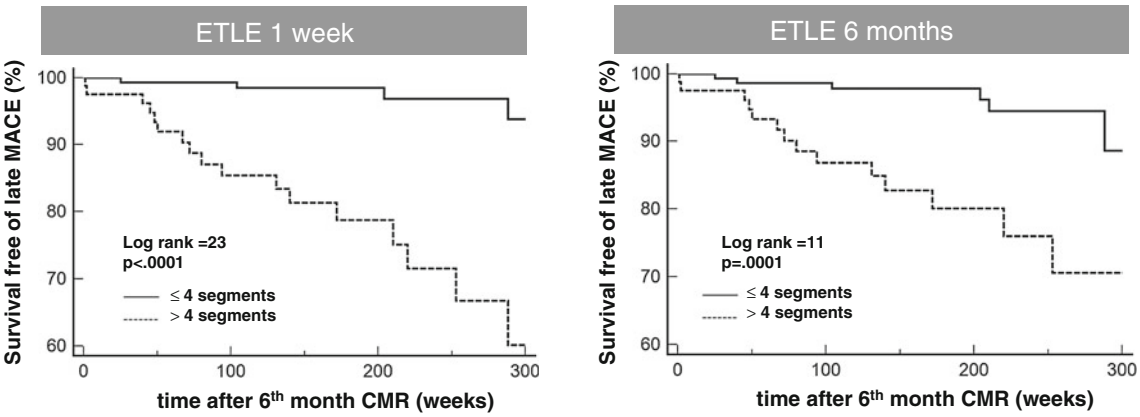
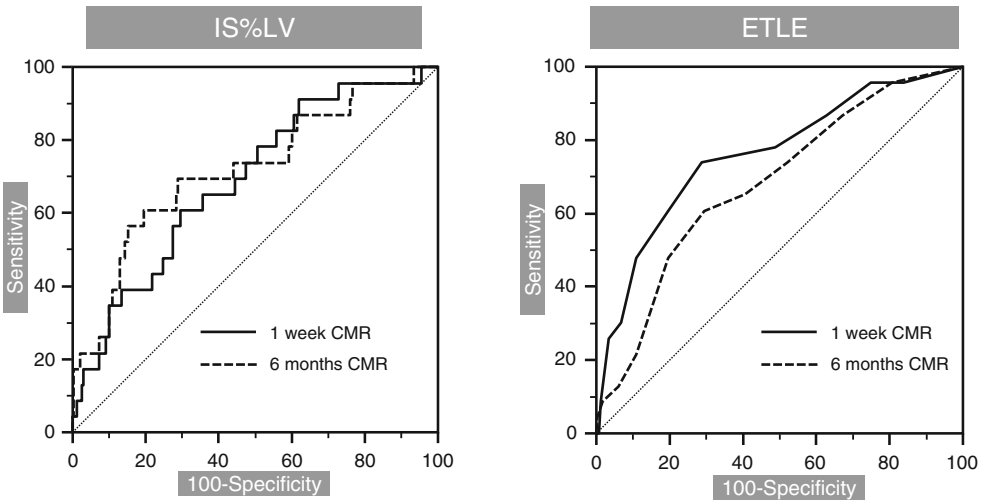


Fig. 4 Kaplan–Meier survival free of late MACE according to the median number of segments showing transmural necrosis at 1 week and 6 months CMR study. *MACE* major adverse cardiac events, *ETLE* extent of transmural late enhancement



	AUC [95%CI]
1 week	.691 [.630-.748]
6 months	.717 [.656-.772]
Comparison of AUC	**p-value**
1 week vs. 6 months	.5

	AUC [95%CI]
1 week	.759 [.701-.811]
6 months	.678 [.616-.736]
Comparison of AUC	**p-value**
1 week vs. 6 months	.1

Fig. 5 Comparison of CMR-derived infarct size at 1 week and 6 months for predicting late MACE. Receiver-operating characteristics curves for the prediction of late MACE of CMR-derived infarct size (% of left ventricular mass and number of segments showing transmural necrosis) at 1 week and 6 months CMR study. *MACE* major adverse cardiac events, *AUC* area under the curve, *95 % CI* 95 % confidence interval, *CMR* cardiovascular magnetic resonance, *LV* left ventricular, *ETLE* extent of transmural late enhancement

However, whether or not the remaining scar size at a follow-up CMR study or the magnitude of infarct size regression offers additional prognostic value beyond the information obtained at 1 week has not yet been evaluated. Moreover, in times of economical shortage the question whether or not to perform additional CMR studies for prognostic purposes has gained importance.

The prognostic value of a comprehensive CMR study shortly after STEMI has been well established [7, 8]. In the present study, we systematically performed CMR at 1 week and 6 months after STEMI in an unselected population and assessed the value of scar size at both time points to predict late MACE (all MACE occurring from 6 months after STEMI onwards). Our data show that, both 1 week and 6 months CMR LGE parameters, separately analyzed in the univariate analyses, were associated with late MACE. Nevertheless after rigorous adjustment for baseline and angiographic characteristics and taking into account 1 week CMR variables, no CMR variable from 6 months persisted in the multivariable analysis. The ETLE at 1 week resulted to be the strongest prognostic infarct size index, which is in line with previous data [5, 28, 29].

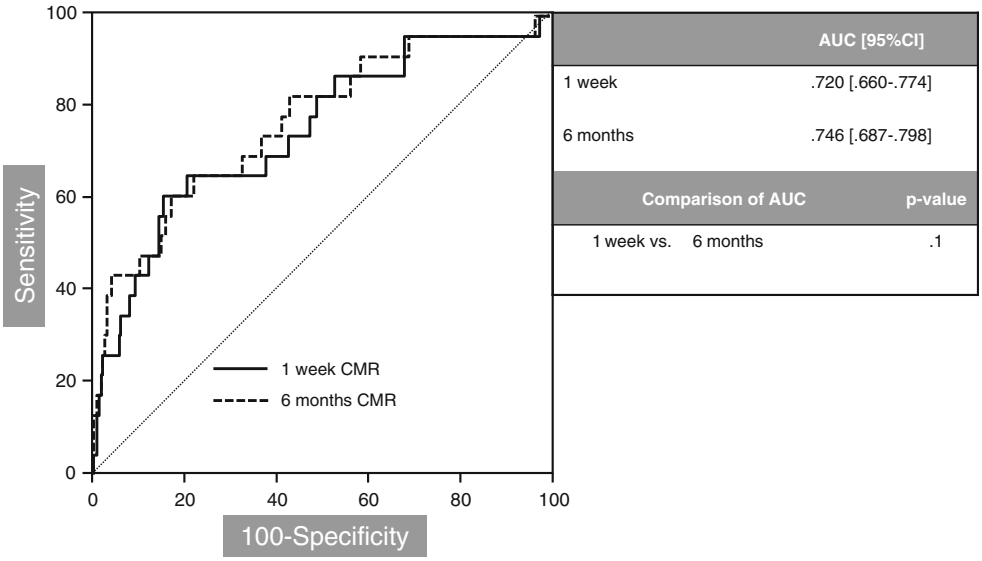


Fig. 6 C-Statistic of CMR multivariable models at 1 week and 6 months for predicting late MACE. Comparison of the predictive value of a model containing clinical and angiographic variables and variables derived from 1 week and 6 months CMR study. *CMR* cardiovascular magnetic resonance, *MACE* major adverse cardiac events, *AUC* area under the curve, *95 % CI* 95 % confidence interval

Table 4 Unadjusted and multivariable adjusted predictors of late MACE using variables available at 1 week (model 1) and both 1 week and 6 months (model 2)

	Adjusted HR [95 % CI][b]	*p* value
Model 1 (containing variables from 1 week with $p < .05$ in the univariate analysis)		
Previous coronary artery disease	13.893 [3.991–48.361]	<.0001
Heart rate (beats per minute)[a]	1.016 [1.000–1.032]	.052
Median peak creatine kinase-MB (ng/ml)[a]	1.000 [.999–1.001]	.78
Anterior infarction	1.616 [.477–5.471]	.441
Final myocardial blush grade 2–3	.718 [.271–1.902]	.718
1 week LV ejection fraction (%)[a]	.998 [.951–1.046]	.923
1 week ETLE (number of segments)[a]	1.313 [1.135–1.519]	<.0001
1 week IS%LV[a]	1.003 [.960–1.048]	.907
Model 2 (containing variables from 1 week and 6 months with $p < .05$ in the univariate analysis)		
Previous coronary artery disease	13.893 [3.991–48.361]	<.0001
Heart rate (beats per minute)[a]	1.016 [1.000–1.032]	.052
Median peak creatine kinase-MB (ng/ml)[a]	1.000 [.999–1.001]	.920
Anterior infarction	1.620 [.462–5.683]	.451
Final myocardial blush grade 2–3	.649 [.239–1.765]	.397
1 week LV Ejection fraction (%)[a]	1.020 [.958–1.087]	.532
1 week ETLE (number of segments)[a]	1.313 [1.135–1.519]	<.0001
1 week IS%LV[a]	.987 [.937–1.041]	.636
6 months LV Ejection fraction (%)[a]	.974 [.922–1.029]	.342
6 months ETLE (number of segments)[a]	.700 [.487–1.005]	.053
6 months IS%LV[a]	1.062 [.976–1.155]	.162

MACE major adverse cardiac events, *LV* left ventricular, *HR* hazard ratio,*95 % CI* 95 % confidence interval, *ETLE* no. of segments with transmural (in more than 50 % of wall thickness) late gadolinium enhancement, *IS%LV* infarct size expressed as a percentage of LV

[a] Per each unit increase

[b] Cox regression analysis adjusted for variables yielding a *p* value <.05 in tables 1 and 3

A notable and novel finding of the present study is the lack of a significant association of infarct size regression with late MACE. This finding might be explained by the fact that patients with late MACE displayed significantly larger CMR-derived infarct size indexes already at 1 week. The amount of regression was comparable to patients without late MACE resulting in persisting larger scar sizes at 6 months.

Timing of CMR after STEMI

Post-infarction imaging by CMR has mainly been carried out around 1 week after STEMI [6, 7] and current guidelines recommend a pre-discharge CMR, among other imaging modalities, for the assessment of myocardial viability [30]. One week after myocardial infarction seems to be the ideal time point for the assessment of the status of

the microcirculation [31]. The present study shows for the first time that, as far as prognosis is concerned, CMR-derived infarct size at a later time point does not offer incremental prognostic value, highlighting the importance of a 1 week CMR. Additionally, a CMR study in the acute phase also offers additional information derivable from T2 sequences, namely myocardial salvage and the area at risk, which in turn have shown to possess predictive value for adverse outcome [32] and LV remodelling [33]. Since myocardial edema [34] and MVO disappear during the time course after STEMI, later CMR studies fail to assess these important parameters. Moreover, an early study evidently permits short-term prognostication and in the present study 14 MACE occurred before the 6 month CMR study was performed.

Clinical implications

According to the present data, several conclusions for the clinical practice can be made: CMR-derived infarct size at 1 week after STEMI offers the highest value as far as prognosis is concerned. Although individually associated with late MACE, CMR-derived scar size at a repeated study at 6 months does not offer relevant incremental prognostic information. Therefore, routine CMR re-examination of STEMI patients at 6 months for prognostic purposes does not appear feasible, especially in times of economic shortage. To date recent STEMI guidelines [30] acknowledge the usefulness of CMR after STEMI in patients in whom echocardiography is not feasible with a Class IIbC recommendation. However, since in the setting of myocardial stunning, for the assessment of exact infarct size and remaining myocardial viability and the prognostic implications presented in this study, CMR may be the ideal modality. Nevertheless, it has to be stressed that in selected cases a repetition of CMR during follow up after STEMI can be highly warranted for the evaluation of LV remodelling, residual myocardial damage hence viability, global systolic function and in order to indicate the implantation of an implanted cardioverter/defibrillator.

Limitations

There are some limitations in the present study that might limit the applicability of our findings into clinical routine. Firstly, the exclusion of unstable patients and the fact that presence of prior infarction was based on patient history pose a potential bias. Secondly, though the patient population of the present study reflects a "typical" STEMI population, it remains to be determined whether the results may be transferred to more elderly patients with larger infarctions. Thirdly, patients received medical therapy according to STEMI guidelines, however since we did not document individual adherence to medication we cannot exclude an effect of medical therapy on MACE rate.

Conclusions

CMR-derived scar size determined by a repeated CMR scan at 6 months after STEMI, though associated with late MACE during follow up, does not offer incremental prognostic value beyond the information obtained with a 1 week CMR study.

Acknowledgments This work was supported by the "Instituto de Salud Carlos III" (PI1102323 grant). O. Husser was supported by the "Regensburger Forschungsförderung in der Medizin (ReForM)".

Conflict of interest No conflict of interest exists in the present study.

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