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Prognostic Value of Strain by Tissue Tracking Cardiac Magnetic Resonance After ST-Segment Elevation Myocardial Infarction

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the prognostic value of strain as assessed by tissue tracking (TT) cardiac magnetic resonance (CMR) soon after ST-segment elevation myocardial infarction (STEMI).

BACKGROUND The prognostic value of myocardial strain as assessed post-STEMI by TT-CMR is unknown.

METHODS The authors studied the prognostic value of TT-CMR in 323 patients who underwent CMR 1 week post-STEMI. Global (average of peak segmental values [%]) and segmental (number of altered segments) longitudinal (LS), circumferential, and radial strain were assessed using TT-CMR. Global and segmental strain cutoff values were derived from 32 control patients. CMR-derived left ventricular ejection fraction, microvascular obstruction, and infarct size were determined. Results were validated in an external cohort of 190 STEMI patients.

RESULTS During a median follow-up of 1,085 days, 54 first major adverse cardiac events (MACE), which included 10 cardiac deaths, 25 readmissions for heart failure, and 19 readmissions for reinfarction were documented. MACE was associated with more severe abnormalities in all strain indexes ($p < 0.001$), although only global LS was an independent predictor ($p < 0.001$). The MACE rate was higher in patients with a global LS of $\geq -11\%$ (22% vs. 9%; $p = 0.001$). After adjustment for baseline and CMR variables, global LS (hazard ratio [HR]: 1.21; 95% confidence interval [CI]: 1.11 to 1.32; $p < 0.001$) was associated with MACE. In the external validation cohort, a global LS $\geq -11\%$ was seen in a higher proportion of patients with MACE (34% vs. 9%; $p < 0.001$). Global LS predicted MACE after adjustment for baseline and CMR variables (HR: 1.18; 95% CI: 1.04 to 1.33; $p = 0.008$). The addition of global LS to the multivariate models, including baseline and CMR variables, did not significantly improve the categorical net reclassification improvement index in either the study group (-0.015; $p = 0.7$) or in the external validation cohort (-0.019; $p = 0.9$).

CONCLUSIONS TT-CMR provided prognostic information soon after STEMI. However, it did not substantially improve risk reclassification beyond traditional CMR indexes. (J Am Coll Cardiol Img 2018;11:1448–57)

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Recent studies have shown that myocardial deformation imaging by speckle tracking echocardiography soon after ST-segment elevation myocardial infarction (STEMI) predicts regional cardiac function recovery (1) and patient outcomes (2,3). Tissue tracking (TT) cardiac magnetic resonance (CMR) is feasible in acute STEMI and promises to be a more accurate method for strain quantification (4,5).

After STEMI, CMR allows for a comprehensive state-of-the-art analysis of the structural consequences of myocardial infarction (6), and CMR indexes have emerged as potent predictors of patient outcomes (7,8). Currently, the prognostic value of the assessment of myocardial strain by TT-CMR soon after STEMI has not been validated. We hypothesized that myocardial strain assessed by TT-CMR permits risk stratification of patients soon after STEMI.

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METHODS

STUDY GROUP. This is a retrospective study based on a large registry of STEMI patients in a tertiary university hospital (6,8). All patients gave written informed consent. The study protocol was approved by the local ethics committee on human research and complies with the 1975 Declaration of Helsinki guidelines. TT-CMR indexes were retrospectively quantified using currently available software.

Criteria for the study group included patients admitted for a first STEMI, which was defined according to current definitions (9), patients treated with percutaneous coronary intervention, and patients who underwent CMR pre-discharge. From 2002 to 2014, we enrolled 542 patients with these characteristics.

Exclusion criteria were death (n = 22), re-infarction (n = 24), severe clinical instability (n = 36) during admission, and any contraindications to CMR, including claustrophobia (n = 19), previous pacemaker (n = 10), the decision of the patient (n = 7), and a history of adverse reactions to gadolinium contrast (n = 3). TT-CMR measurements were performed retrospectively and were not planned when the registry was started. As a consequence, 98 patients had to be excluded because of incomplete or insufficient image acquisition for an accurate offline assessment of all TT-CMR indexes; the number of phases acquired for short- and long-axis images was different in 81 patients, and in 17 patients 1 of the long-axis images needed for calculations was not available. Thus, the final study group consisted of 323 patients.

Baseline characteristics, including the global registry of acute coronary events (10) and Thrombolysis In Myocardial Infarction (TIMI) (11) risk scores, were prospectively registered in all cases. The percutaneous coronary intervention technique was left at the discretion of the interventional operator. TIMI flow grade in the culprit artery (before and after percutaneous coronary intervention) was analyzed in all cases (12). Patients were managed both in-hospital and after discharge by a specific STEMI unit, and current recommendations were strictly followed (9). Further details on patient characteristics are provided in **Table 1**.

CARDIAC MAGNETIC RESONANCE. All patients included in the study group were examined with a 1.5-T System (Sonata Magnetom, Siemens, Erlangen, Germany) 7 ± 2 days after STEMI in accordance with our previously validated study protocol (6,8). CMR studies were analyzed offline by an experienced observer blinded to all patient data using customized software (QMASS MR 6.1.5, Medis, Leiden, the Netherlands). CMR data were prospectively incorporated into the database.

Left ventricular ejection fraction (LVEF) (%), LV end-diastolic volume index (ml/m^2), LV end-systolic volume index (ml/m^2), LV mass index (g/m^2), infarct size (% of LV mass), microvascular obstruction (% of LV mass), myocardial edema (% of LV mass), and myocardial salvage index (% of LV mass with myocardial edema not showing delayed enhancement) were calculated.

Further details on the technical aspects of CMR acquisition, sequences, and quantification can be found in the Online Appendix. Interobserver and intraobserver variability for all CMR indexes used in the present study are shown in Online Tables 1A and 1B, and in Online Figure 1.

TISSUE TRACKING CMR. All strain parameters were quantified offline by an experienced observer blinded to all patient data. These analyses were carried out retrospectively using currently available certified software (CMR42, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada).

On a segmental basis, the 16-segment model was used for calculation of the peak longitudinal strain (LS), circumferential strain (CS), and radial strain (RS) in each segment (13). On a per-patient basis, the global LS, CS, and RS were calculated as the mean of the respective peak values in the 16 segments (**Figure 1**).

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

CS = circumferential strain

EF = ejection fraction

LS = longitudinal strain

LV = left ventricular

MACE = major adverse cardiac event(s)

RS = radial strain

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

TT = tissue tracking

TABLE 1 Baseline Characteristics of the Entire Study Group and of Patients With and Without MACE

	All Patients (N = 323)	MACE (n = 54)	No MACE (n = 269)	p Value
Age, yrs	59 ± 11	63 ± 14	59 ± 11	0.01
Male	268 (83)	43 (80)	225 (84)	0.6
Diabetes mellitus	68 (21)	9 (17)	59 (22)	0.4
Hypertension	154 (48)	30 (56)	124 (46)	0.2
Hypercholesterolemia	147 (46)	25 (46)	122 (45)	0.9
Smoker	182 (56)	32 (59)	150 (56)	0.6
Heart rate on admission, beats/min	79 ± 21	88 ± 25	78 ± 20	<0.001
Systolic pressure, mm Hg	128 ± 30	129 ± 32	128 ± 29	0.9
Killip class				0.009
I	273 (85)	43 (80)	230 (85)	
II	40 (12)	6 (11)	34 (13)	
III	6 (2)	4 (7)	2 (1)	
IV	4 (1)	1 (2)	3 (1)	
Time to reperfusion, min	180 (120-300)	280 (178-424)	210 (120-280)	0.005
Peak creatine kinase MB mass, ng/ml	177 (66-300)	254 (79-423)	161 (60-295)	0.04
Anterior infarction	167 (52)	38 (70)	129 (48)	0.003
Multivessel disease	85 (26)	15 (28)	70 (26)	0.8
TIMI flow grade before PCI				0.9
0	169 (52)	28 (52)	141 (53)	
1	24 (7)	5 (9)	19 (7)	
2	35 (11)	5 (9)	30 (11)	
3	95 (30)	16 (30)	79 (29)	
TIMI flow grade after PCI				0.8
0	4 (1)	0 (0)	4 (1)	
1	1 (1)	0 (0)	1 (1)	
2	26 (8)	5 (9)	21 (8)	
3	292 (90)	49 (91)	243 (90)	
GRACE risk score	136 ± 30	148 ± 31	133 ± 29	0.001
TIMI risk score	2.8 ± 2.2	3.8 ± 2.5	2.6 ± 2.1	<0.001

Values are mean ± SD, n (%), or median (25th to 75th percentile).

GRACE = Global Registry of Acute Coronary Events; MACE = major adverse cardiac event(s); MB = myocardial band; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

For categorical analyses, cutoff values were derived from a control group of 32 patients who underwent CMR for a cardiovascular checkup and who had no evidence of structural cardiac disease.

In summary and based on recent literature (2,3), we used the following sets of strain variables: 1) global LS, CS, and RS: mean of the respective peak values in the 16 segments for each patient (3); 2) number of segments in each patient with altered LS, CS, and RS: number of segments with LS and CS above the respective segmental cutoff values and number of segments with RS below the respective segmental cutoff values (2); and 3) patients were considered to have altered global LS if LS was ≥−11%, altered global CS if CS was ≥−14%, and altered global RS if RS was ≤32%.

Further details on the acquisition of strain indexes and definition of cutoff values can be found in the Online Appendix and in Online Table 2.

EXTERNAL VALIDATION COHORT. Although the operator measuring TT-CMR parameters in the study group was blinded to all patient data, and it was improbable that the retrospective quantification of TT-CMR could exert an influence on the association between strain data with patient outcomes, we decided to confirm our results in an external validation cohort.

The external validation cohort included 190 patients admitted for STEMI in a different tertiary hospital; we used the same inclusion and exclusion criteria as the study group. Patient management, CMR scanner characteristics, CMR studies protocol, and CMR software were the same used in the study group, but studies and quantification were carried out by local personnel. In the external validation cohort, all data, including TT-CMR indexes, were prospectively and immediately incorporated into the database. A local experienced observer blinded to all patient data quantified CMR studies of patients included in the external validation cohort. Further details on the external validation cohort are listed in Online Tables 3 and 4. The association of TT-CMR indexes with the occurrence of major adverse cardiac events (MACE) was explored using the same sets of strain indexes and cutoff values tested in the study group.

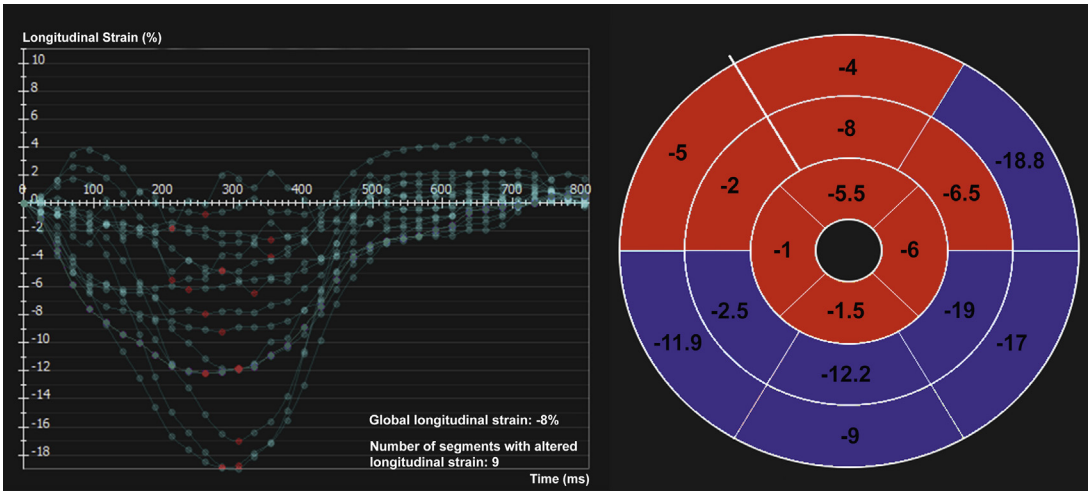
ENDPOINT AND FOLLOW-UP. The endpoint was time to first MACE and included a composite of cardiac death, readmission for heart failure, or readmission for reinfarction, whichever occurred first. Current definitions were applied (14,15).

As secondary endpoints, we examined the association of altered TT-CMR indexes with: 1) time to the occurrence of cardiac death, readmission for heart failure, and readmission for reinfarction separately in the whole study group; and 2) time to the occurrence of the first MACE in patients with TIMI flow grade 3 after percutaneous coronary intervention (after 31 patients with TIMI flow grade <3 after percutaneous coronary intervention were excluded from the study group).

All MACE were systematically reviewed, and consensus among 3 cardiologists was required to classify a cardiac event.

STATISTICAL ANALYSIS. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Continuous normally distributed data were expressed as the mean ± SD and compared using the unpaired Student's *t* test. Nonparametric data were expressed as the median (interquartile range) and

FIGURE 1 Tissue Tracking–Cardiac Magnetic Resonance Assessment



Longitudinal strain throughout the cardiac cycle in the 16 segments of a patient with a large anterior infarction. **Red points** indicate the peak strain values in the respective segments. On a per patient basis, global strain (% deformation) was calculated as the mean of the respective peak values in the 16 segments **(left panel)**. The number of segments displaying abnormal strain (in comparison with segmental values in control patients) was also determined **(right panel)**.

compared using the Mann-Whitney *U* test. Group percentages were compared using the chi-square test or Fisher exact test, where appropriate. In the univariate analyses, the associations of global strain variables with time to the first MACE, time to cardiac death, time to readmission for heart failure, and time to readmission for reinfarction were assessed using Kaplan-Meier curves and the log-rank test.

We performed a first multivariable analysis to test the association of the 6 strain indexes with time to MACE using a multivariable Cox proportional hazard regression model. In this model, the only strain index independently associated with the time to MACE was global LS. To avoid variable overfitting, for subsequent multivariable analyses, global LS was the only strain parameter tested.

The association of global LS with time to MACE adjusted for baseline and CMR variables was assessed using multivariable Cox proportional hazard regression models. The variables adjusted for in the multivariable models to predict time to MACE were identified by comparing patients who did and who did not exhibit MACE during follow-up; variables with a p value < 0.1 were included in the regression models as cofactors. Hazard ratios with the corresponding 95% confidence intervals were computed. The proportional hazards assumption based on Schoenfeld's residuals was considered to be accomplished if the p value was >0.05.

From a clinical point of view and to avoid variable overfitting of the final multivariable model, we carried out the following steps: 1) first, a multivariable model (Model 1: baseline characteristics) was tested, including those baseline variables that showed an association ($p < 0.1$ in **Table 1**) with the occurrence of MACE; 2) a second multivariable model (Model 2: baseline characteristics plus CMR indexes) included variables from Model 1 independently related to the occurrence of MACEs plus CMR indexes that showed an association with MACE ($p < 0.1$ in **Table 2**); and 3) the final multivariable model (Model 3: baseline characteristics plus CMR indexes plus global LS) included variables from Model 2 that were independently related to the occurrence of MACE plus global LS. Colinearity of variables tested in the final multivariate Model 3 (independent variables selected in Model 2 plus global LS) was assessed using the tolerance statistic (excessive if <0.20) and the variance inflation factor (excessive if >5) (16). The correlation matrix, including global LS, all CMR indexes, and independent variables in Model 3, was also obtained.

Changes in the discrimination accuracy (c-statistic) and in risk reclassification (using the categorical net reclassification improvement index and the respective frequency data) when global LS was included in the final multivariable model (Model 3 vs. Model 2)

TABLE 2 Cardiac Magnetic Resonance Characteristics of the Entire Study Group and of Patients With and Without MACE

	All Patients (N = 323)	MACE (n = 54)	No MACE (n = 269)	p Values
LVEF, %	53 ± 13	45 ± 15	54 ± 12	<0.001
LV end-diastolic volume index, ml/m^2	80 ± 24	84 ± 28	79 ± 23	0.2
LV end-systolic volume index, ml/m^2	39 ± 22	49 ± 26	37 ± 20	0.005
LV mass, g/m^2	74 ± 19	76 ± 18	74 ± 19	0.4
Edema, % of LV mass	30 ± 17	37 ± 18	28 ± 17	0.001
Microvascular obstruction, % of LV mass	0 (0.0-2.4)	0.2 (0.0-2.7)	0 (0.0-2.4)	0.05
Infarct size, % of LV mass	22 ± 15	28 ± 18	20 ± 14	0.003
Myocardial salvage index, %	22 (2.5-46.0)	15.5 (1.5-40.0)	23 (2.9-48.0)	0.4

Values are mean ± SD or median (25th to 75th percentile).
LV = left ventricular; LVEF = left ventricular ejection fraction; MACE = major adverse cardiac event(s).

were computed both for the study group and for the external validation cohort.

Statistical significance was considered a 2-tailed $p < 0.05$. The SPSS statistical package version 15.0 (SPSS Inc., Chicago, Illinois) and STATA version 9.0 (StataCorp, College Station, Texas) were used.

RESULTS

From the initial study group of 323 patients with a median follow-up of 1,085 days (range 14 to 4,711 days), we documented 54 patients with first MACE, including 10 cardiac deaths, 25 readmissions for heart failure, and 19 readmissions for reinfarction.

Baseline characteristics and cardiac catheterization variables associated with the occurrence of MACE are displayed in Table 1.

Table 2 depicts the state of traditional CMR parameters in the whole study group and in patients with and without MACE during follow-up.

TISSUE TRACKING CMR AND MACE. Table 3 shows the characteristics of the 6 strain indexes determined in the whole study group and in patients with and without MACE during follow-up. Patients with MACE displayed a higher number of segments with abnormal LS, CS, and RS ($p < 0.001$ for all comparisons). Similarly, patients with MACE during follow-up exhibited higher values of global LS and global CS, and lower values of global RS ($p < 0.001$ for all comparisons).

TABLE 3 Strain Characteristics of the Entire Study Group and of Patients With and Without MACE

	All Patients (N = 323)	MACE (n = 54)	No MACE (n = 269)	p Value
Segments with altered CS, n	9.7 ± 3.7	11.3 ± 3.6	9.4 ± 3.6	<0.001
Segments with altered LS, n	9.3 ± 3.7	11.5 ± 3.6	8.8 ± 3.6	<0.001
Segments with altered RS, n	9.7 ± 3.6	11.2 ± 3.6	9.3 ± 3.6	<0.001
Global CS, %	−13.7 ± 4.3	−11.4 ± 4.4	−14.2 ± 4.2	<0.001
Global LS, %	−10.1 ± 3.4	−8.1 ± 3.2	−10.5 ± 3.3	<0.001
Global RS, %	24.9 ± 10.1	20.4 ± 9.8	25.9 ± 10.0	<0.001

Values are mean ± SD. Cutoff values for considering the presence of abnormal segmental strain are listed in Online Table 2.
CS = circumferential strain; LS = longitudinal strain; MACE = major adverse cardiac event(s); RS = radial strain(s).

Figure 2 shows the MACE-free survival curves. Patients with global LS ≥−11%, global CS ≥−14%, and global RS ≤32% displayed a significantly higher risk of MACE during follow-up ($p < 0.05$ for all comparisons).

A similar tendency was observed when these same analyses were carried out separately for cardiac death, readmission for heart failure, and readmission for reinfarction (Online Figures 2A to 2C).

Similar to results in the whole study group, in patients with TIMI flow 3 after percutaneous coronary intervention (n = 292), those with global LS ≥−11%, global CS ≥−14%, and global RS ≤32% displayed a significantly higher risk of MACE during follow-up ($p < 0.05$ for all comparisons) (Online Figure 3).

MULTIVARIABLE ANALYSES. To simplify data management and to select the strain index with the highest prognostic value, we carried out a preliminary multivariable analysis that included only the 6 TT-CMR indexes determined in the present study. Of these, global LS was the only one found to be independently associated with MACEs (Table 4).

We aimed to determine whether global LS was significantly associated with MACE once adjusted for baseline characteristics and for those CMR indexes that were independently related to the occurrence of MACE (Table 5). In the final multivariable model (Table 5), the variables associated with MACE were time to reperfusion, the TIMI risk score, and global LS. The proportional hazards assumption of the final multivariate model was not violated ($p = 0.8$).

Regarding colinearity, all variables tested in the final multivariate model (LVEF, time to reperfusion, the TIMI risk score, and global LS) showed a tolerance statistic of >0.20 and a variance inflation factor of <5 (Table 5 footnote). A negative correlation ($r = -0.7$) existed between global LS and LVEF. The correlation matrix is provided in Online Table 5.

EXTERNAL VALIDATION COHORT. Baseline and CMR characteristics of patients with (n = 28) and without MACE (n = 162) in the external validation cohort are listed in Online Tables 3 and 4.

As with the study group, patients with MACE in the external validation cohort also displayed higher global LS and CS values, and lower RS values ($p < 0.05$ for all comparisons) (Table 6).

As shown in **Figure 3**, patients in the external validation cohort with global LS ≥−11% displayed a significantly higher risk of MACE during follow-up (34% vs. 9%; $p < 0.001$).

Finally, as with the study group, global LS was significantly associated with the occurrence of MACE in the external validation cohort after adjustment for baseline characteristics and CMR indexes (1.18; 95% CI: 1.04 to 1.33; $p = 0.008$) (Online Table 6). The proportional hazards assumption of the final multivariate model was not violated ($p = 0.2$). All variables tested in the final multivariate model showed a tolerance statistic of >0.20 and a variance inflation factor of <5 (Online Table 6 footnote).

CHANGES IN DISCRIMINATION ACCURACY AND IN RISK RECLASSIFICATION. In the study group, when compared with the multivariate model that tested baseline and traditional CMR indexes without global LS (Model 2 in **Table 5**), the final multivariate model that included global LS (Model 3 in **Table 5**) did not significantly improve the discrimination accuracy as derived from the c-statistics (Model 2: 0.69; 95% CI: 0.59 to 0.79; Model 3: 0.70; 95% CI: 0.60 to 0.79; $p = 0.7$) nor the risk reclassification as derived from the categorical net reclassification improvement index (−0.015; $p = 0.7$) (**Table 7**).

Similar results were detected in the external validation cohort (Online Table 7).

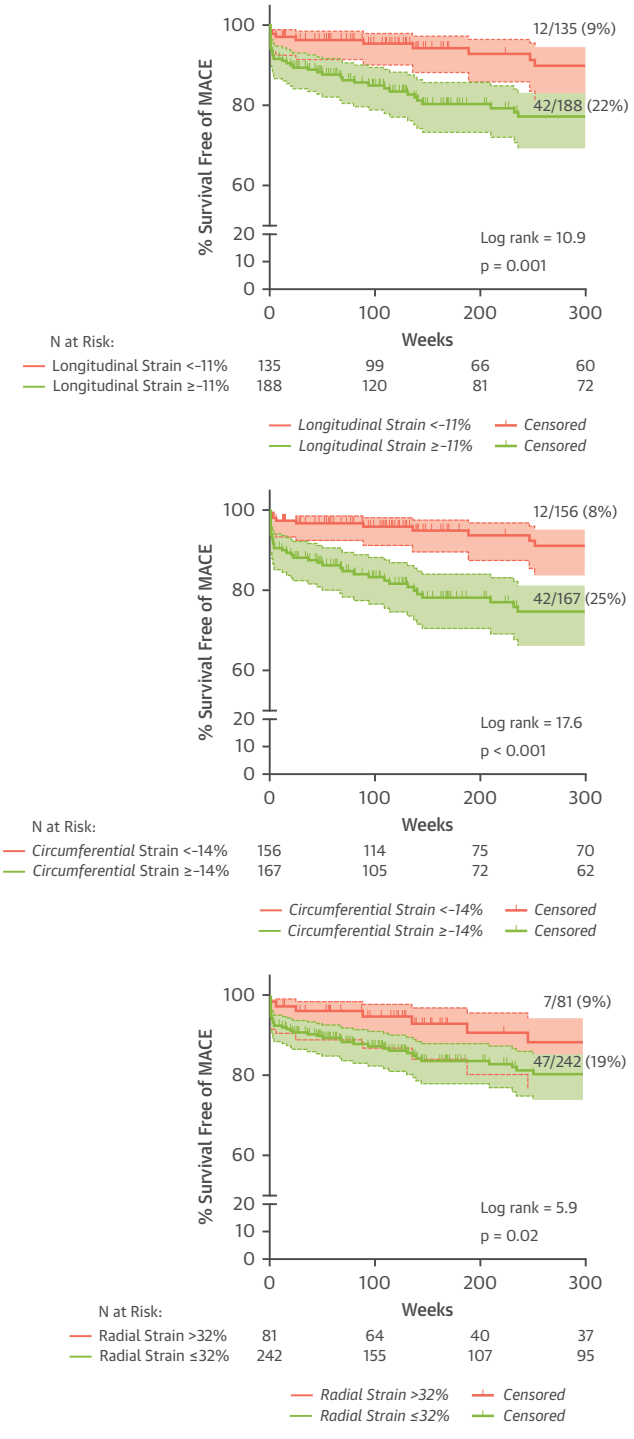
DISCUSSION

The main finding of the present study was that myocardial strain as derived from TT-CMR contributes significant prognostic information to stratify risk soon after STEMI. However, it did not substantially improve the risk reclassification of patients compared with the information provided by the baseline characteristics of patients and traditional CMR indexes.

MYOCARDIAL STRAIN BY ECHOCARDIOGRAPHY AND PROGNOSIS AFTER STEMI. Echo-derived myocardial strain has been shown to be a good predictor of outcome in a variety of clinical settings (3). In patients with a recent myocardial infarction (either with or without ST-segment elevation), Wang et al. (2) and Ersboll et al. (3) showed that a more severely altered global LS was associated with cardiovascular death or heart failure hospitalization. In a group of 391 STEMI patients, Biering-Sørensen et al. (17) demonstrated that regional longitudinal myocardial deformation appeared to be a paramount marker of adverse outcome.

The prognostic value of TT-CMR in STEMI patients has not yet been analyzed. Moreover, whether

FIGURE 2 Kaplan-Meier Curves With 95% CIs Representing the Survival Free of MACEs in Patients of the Study Group With and Without Altered Global LS, CS, and RS



Patients with altered global longitudinal strain (LS), circumferential strain (CS), and radial strain (RS) displayed a significantly higher risk of a first major adverse cardiac event (MACE). **Solid lines** represent the survival curves and the **upper and lower lines of the colored areas** correspond to the 95% confidence intervals (CIs).

TABLE 4 Predictors of MACE: Multivariable Study of Strain Variables

	Odds Ratio (95% CI)	p Value
Segments with altered CS, n	0.88 (0.56–1.38)	0.60
Segments with altered LS, n	1.14 (0.91–1.41)	0.30
Segments with altered RS, n	1.12 (0.73–1.71)	0.70
Global CS, %	1.25 (0.89–1.77)	0.90
Global LS, %	1.25 (1.14–1.36)	<0.001
Global RS, %	1.08 (0.96–1.22)	0.50

To avoid variable overfitting and to select the strain variable with the highest prognostic value, the first multivariable analysis included only strain indexes.

CI = confidence interval; other abbreviations as in Tables 1 and 3.

myocardial strain (either by echocardiography or by CMR) provides information once adjusted for potent CMR markers remains uncertain.

TABLE 5 Predictors of MACE: Multivariable Study

	Hazard Ratio (95% CI)	p Value
Model 1: baseline characteristics		
Age, yrs	1.03 (0.99–1.07)	0.30
Heart rate on admission, beats/min	1.020 (1.002–1.030)	0.10
Killip class I	—	—
Killip class II vs. I	0.15 (0.01–1.77)	0.10
Killip class III vs. I	0.12 (0.01–1.35)	0.09
Killip class IV vs. I	2.47 (0.24–25.05)	0.40
Time to reperfusion, min	1.001 (1.0004–1.001)	<0.001
Peak creatine kinase MB mass, ng/ml	1.000 (1.000–1.001)	0.40
Anterior infarction	2.02 (1.10–3.70)	0.02
GRACE risk score	0.99 (0.98–1.01)	0.30
TIMI risk score	1.22 (1.09–1.37)	<0.001
Model 2: baseline characteristics + CMR indexes		
Time to reperfusion, min	1.001 (1.0003–1.001)	<0.001
Anterior infarction	1.38 (0.70–2.70)	0.30
TIMI risk score	1.20 (1.08–1.35)	0.001
LVEF, %	0.96 (0.94–0.98)	<0.001
LV end-systolic volume index, ml/m^2	0.99 (0.97–1.008)	0.30
Edema, % of LV mass	1.01 (0.99–1.04)	0.30
Microvascular obstruction, % of LV mass	1.01 (0.96–1.07)	0.80
Infarct size, % of LV mass	0.99 (0.96–1.02)	0.90
Model 3: baseline characteristics + CMR indexes + Global LS		
Time to reperfusion, min	1.001 (1.0004–1.001)	<0.001
TIMI risk score	1.17 (1.04–1.31)	0.008
LVEF, %	0.99 (0.96–1.02)	0.40
Global LS, %	1.21 (1.11–1.32)	<0.001

Model 1: Baseline characteristics includes the 8 baseline variables showing an association ($p < 0.1$ in Table 1) with the occurrence of MACE. Model 2: Baseline characteristics plus CMR indexes includes variables from Model 1 independently related to the occurrence of MACE plus CMR indexes showing an association with MACE ($p < 0.1$ in Table 2). Model 3: Baseline characteristics plus CMR indexes plus global LS includes variables from Model 2 independently related to the occurrence of MACE plus global longitudinal strain. The hazard ratios with the corresponding 95% CIs are displayed for each model. For the categorical variable Killip class, Killip class = I was considered as the normal reference value. Colinearity of variables tested in Model 3 was as follows: time to reperfusion: tolerance statistic 0.99; variance inflation factor 1.01. TIMI risk score: tolerance statistic 0.88; variance inflation factor 1.13. LVEF: tolerance statistic 0.37; variance inflation factor 2.71; global LS: tolerance statistic 0.35; variance inflation factor 2.83.

Abbreviations as in Tables 1 to 4.

TABLE 6 Strain Characteristics of Patients With and Without MACE in the External Validation Cohort

	MACE (n = 28)	No MACE (n = 162)	p Values
Segments with altered CS, n	6.8 ± 2.7	5.7 ± 2.7	0.05
Segments with altered LS, n	6.0 ± 3.6	3.5 ± 2.7	0.001
Segments with altered RS, n	6.8 ± 3.0	5.6 ± 2.7	0.03
Global CS, %	−15.5 ± 4.8	−18.2 ± 3.9	0.002
Global LS, %	−11.3 ± 4.0	−14.2 ± 3.0	0.001
Global RS, %	36.0 ± 14.8	42.1 ± 12.5	0.02

Values are mean ± SD. Cutoff values for considering the presence of abnormal segmental strain are listed in Online Table 2.

Abbreviations as in Table 3.

MYOCARDIAL STRAIN BY TT-CMR AND PROGNOSIS AFTER STEMI. Myocardial strain measured by myocardial tissue tagging as assessed by CMR has been considered the gold standard for determining myocardial deformation and function. However, tagging has some limitations, such as the fact that it requires the acquisition of additional sequences and time-consuming post-processing (4).

Strain-encoded imaging was introduced to overcome the limitations of tagging. It permits strain quantification directed orthogonal to the image plane. Its value in predicting cardiac events (18) and late systolic recovery (19), as well as detecting significant coronary disease, was proven (19). However, the use of this technique in routine CMR has so far been limited (20).

TT-CMR holds promise to become the gold standard method for strain quantification. It tracks features of interest along contour lines on routinely acquired cine images, analogous to echocardiographic speckle tracking (4,5). Due to the excellent spatial resolution of CMR, limitations related to image quality are almost nonexistent. TT-CMR predicts late systolic recovery soon after infarction (5), and compared with tagging it, it provides better myocardial tracking, greater interobserver agreement, faster analysis, and stronger correlation with infarct size (4).

Universal cutoff values are far from being established for TT-CMR, and considerable intervendor (21), intercenter, and interobserver variability may exist (20). In the present study, interobserver and intraobserver variability were rigorously assessed, and the cutoff values derived from the study group were prospectively validated in an external cohort.

In univariate analyses, abnormalities in patients with MACE were more severe for all strain indexes. Global LS emerged as the only strain parameter independently related to MACE. LS was suggested to be the most appropriate strain modality by echocardiography

in ischemic patients (2,3,17). Based on these observations and on our own results, we only included global LS in subsequent multivariable analyses.

We found that global LS as derived from TT-CMR was associated with the occurrence of MACE. After a comprehensive adjustment for baseline and traditional CMR indexes, only 2 additional robust variables contributed significant information to predict the combined endpoint: time to reperfusion and the TIMI risk score upon presentation. The present study demonstrated the prognostic value of global LS by TT-CMR on highly relevant endpoints in a homogeneous STEMI population. The prospective confirmation in an external validation cohort strengthened our results.

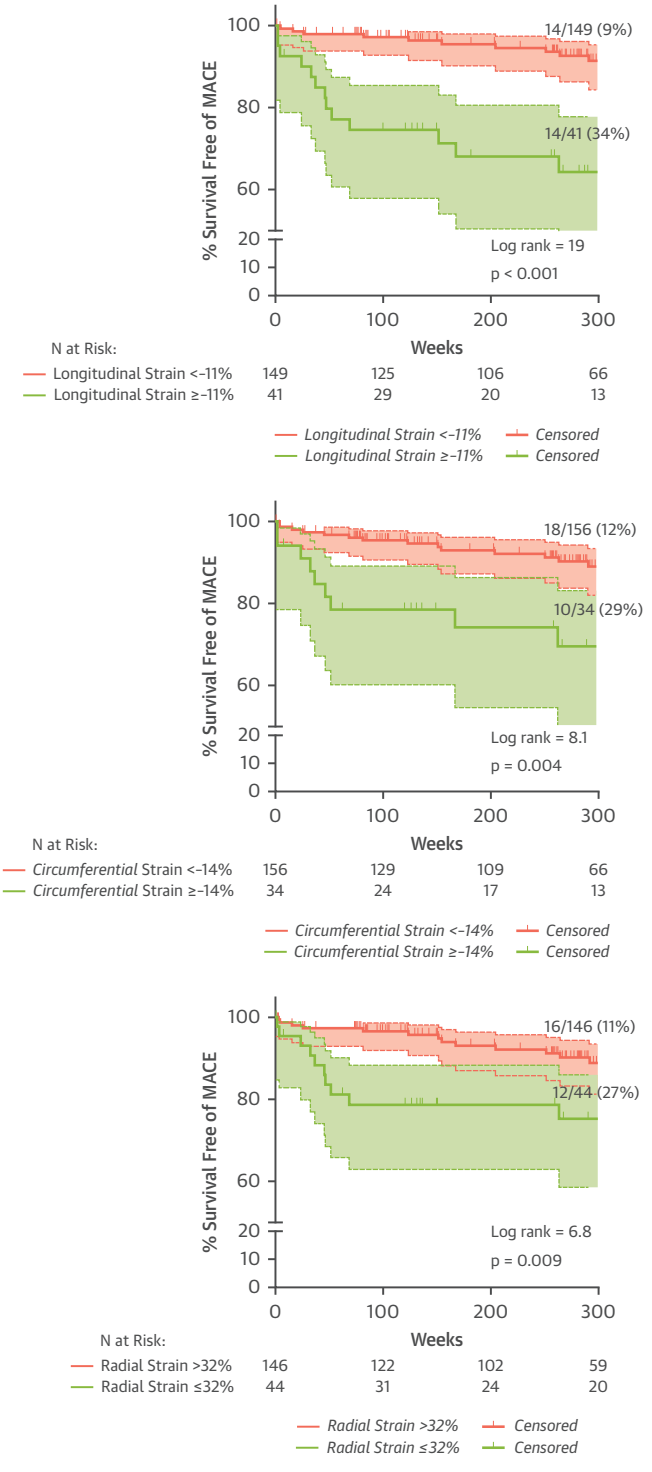
CLINICAL IMPLICATIONS. Although global LS was selected as an independent predictor by the final multivariate models in both the study group and in the external validation cohort, these models did not significantly improve the discrimination accuracy and risk reclassification compared with models that included baseline characteristics and routinely used CMR variables but not global LS. Two factors underlined this observation: 1) the robustness of clinical scores and current technology (in this case, the traditional CMR indexes) for prognostic purposes made it increasingly difficult to achieve substantial improvements in risk prediction by the addition of novel indexes (22); and 2) the presence of colinearity between global LS and LVEF might hamper the additional discriminative power of global LS.

The correlation between the new predictor and the existing variables had a complicated relationship with improvement in discrimination. Testing in new models variables that did not show excessive colinearity with the existing model (tolerance statistic >0.20 and variable inflation factor <5) is warranted (16). This condition was accomplished in the case of global LS and justified the inclusion of global LS in the final multivariate model.

Furthermore, the additional value of a new predictor that was highly and specifically negatively correlated with the existing predictors (as global LS with respect to LVEF, r = −0.7) should be explored, because in some settings it could lead to gains in discrimination (23). Global LS was eventually strongly associated with outcomes, but it did not improve discrimination.

The presented data indicated that TT-CMR could be used in routine CMR measurements for prognostic purposes in post-STEMI patients. However, noting the lack of improvement in discrimination, together

FIGURE 3 Kaplan-Meier Curves With 95% CIs Representing Survival Free of MACEs in Patients of the External Validation Cohort With and Without Altered Global LS, CS, and RS



Patients with altered global LS, CS, and RS displayed a significantly higher risk of a first MACE. **Solid lines** represent the survival curves and the **upper and lower lines of the colored areas** correspond to the 95% CIs. Abbreviations as in Figure 2.

TABLE 7 Cross Tabulation of Predicted Risk With and Without Global LS Among Individuals With and Without Events in the Study Group

	Model 3		
MACE	**Nonevent**	**Event**	**Total**
Model 2			
Nonevent			
Nonevent	200	10	210
Event	16	43	59
Total	216	53	269
Event			
Nonevent	19	0	19
Event	2	33	35
Total	21	33	54

Categorical net reclassification improvement index = −0.015 (p = 0.7). Model 2 included baseline characteristics and CMR indexes. Model 3 included baseline characteristics, CMR indexes and global LS. To calculate the categorical net reclassification improvement index, participants were divided into 2 risk categories (<20% and ≥20%).

Abbreviations as in Tables 1 and 3.

with the large body of scientific evidence that supported the prognostic value of LVEF, infarct size, and microvascular obstruction derived from routine CMR after STEMI (7,8), our interpretation was that TT-CMR could supplement, but not substitute, the use of these consolidated indexes. Further studies and larger series of patients will be needed to determine the exact role of myocardial strain by TT-CMR to guide risk stratification and management of STEMI patients.

STUDY LIMITATIONS. Due to the inherent limitations in the use of CMR after STEMI and the retrospective quantification of TT-CMR in the study group, a high dropout rate occurred (219 of 542 patients initially included in the registry). Moreover, changes in the medical and invasive management of STEMI patients applied throughout the long period of inclusion could have exerted a dynamic influence on some of the CMR indexes evaluated and on patient outcomes. Thus, we could not discard that these and other factors exerted residual confounding on our results.

CONCLUSIONS

In STEMI patients studied with CMR, offline assessment of global LS by TT-CMR can be useful in the prediction of cardiac events but does not substantially improve risk stratification compared with routinely used CMR indexes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The prognostic value of myocardial strain as derived from TT-CMR has not yet been validated. In the present study, we demonstrated the prognostic value of global LS derived from TT-CMR for predicting the clinical course in a large cohort of STEMI patients and in an external validation cohort. However, this index did not substantially improve risk stratification compared with the information provided by baseline characteristics plus traditional CMR variables.

TRANSLATIONAL OUTLOOK: TT-CMR promises to become a new reference technique for assessing global and segmental myocardial strain. In STEMI patients studied with CMR, consideration of offline assessment of global LS by TT-CMR may be warranted for risk stratification. In the setting of STEMI, further studies will be needed to elucidate the exact role of TT-CMR beyond routinely used CMR indexes.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.