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ORIGINAL ARTICLE
Vascular and cardiac imaging

Cardiac magnetic resonance imaging improves prognostic stratification of patients with ST-elevation myocardial infarction and preserved ejection fraction

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Aims To evaluate the prognostic validity of clinical risk factors as well as infarct characterization and myocardial deformation by cardiac magnetic resonance (CMR) in ST-elevation myocardial infarction (STEMI) patients with preserved left ventricular ejection fraction (LVEF) following primary percutaneous coronary intervention (PCI).

Methods and results This multicentre, individual patient-data analysis from two large CMR trials included 1247 STEMI patients. Cardiac magnetic resonance examinations were conducted 3 [interquartile range (IQR) 2–4] days after PCI. LVEF, infarct size, microvascular obstruction (MVO), and myocardial strain values were measured. Primary endpoint was defined as composite of major adverse cardiovascular events (MACE) including death, re-infarction, and congestive heart failure. A preserved LVEF (defined as LVEF ≥50%) was observed in 724 patients (=58%). In the overall cohort, 97 patients experienced a MACE event [follow-up time 12 (IQR 12–13) months], and 34 MACE events occurred in the group with preserved LVEF (5% vs. 12% incidence rate in patients with LVEF < 50%). TIMI risk score [hazard ratio (HR) 1.28, 95% confidence interval (CI) 1.02–1.59; $P = 0.03$] and female gender (HR 2.24, 95% CI 1.10–4.57; $P = 0.03$) emerged as independent clinical determinants of MACE in the patient group with preserved LVEF. Among CMR parameters, the presence of MVO (HR 2.39, 95% CI 1.05–5.46; $P = 0.04$) and reduced global longitudinal strain (GLS; HR 1.12, 95% CI 1.02–1.23; $P = 0.02$) independently predicted MACE in the LVEF-preserved population. The addition of MVO and GLS to the clinical prognostic markers (TIMI risk score, female gender) increased ($P = 0.02$) the prognostic validity [AUC 0.76 (95% CI 0.73–0.79)] compared to the clinical markers alone [AUC 0.65 (0.62–0.69)].

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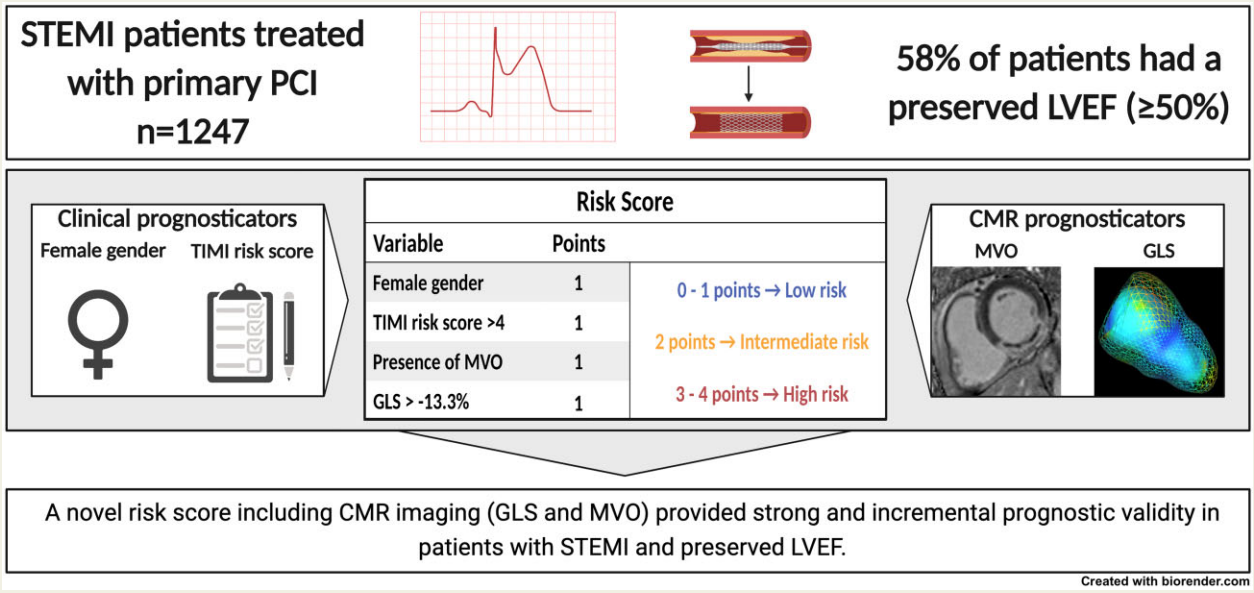
Conclusion In contemporary treated STEMI patients showing preserved LVEF, a CMR-based risk prediction approach assessing MVO and GLS provided strong prognostic value that was incremental to clinical outcome parameters.

Graphical Abstract



Keywords ST-elevation myocardial infarction • Preserved ejection fraction • Cardiac magnetic resonance

INTRODUCTION

Contemporary guidelines recommend left ventricular ejection fraction (LVEF) as principal measure for risk stratification and clinical decision making in patients with ST-elevation myocardial infarction (STEMI).[1] LVEF is, however, only a marker of global systolic function, whereas more subtle differences in LV function cannot be depicted.[2] Significant regional wall motion abnormalities may be present despite preserved LVEF.[3] Moreover, in the current era of primary percutaneous coronary intervention (PCI), a considerable portion of STEMI patients exhibit a near-normal or even preserved LVEF (~50% of all STEMI patients have an LVEF ≥50%).[4] Importantly, based on the large group size, the absolute number of major adverse cardiovascular events (MACE) is substantial in this subgroup with preserved LVEF (up to 70% of all MACE events are reported to occur in the STEMI subgroup with LVEF ≥ 50%),[5] emphasizing the limited prognostic validity of LVEF as well as highlighting the need for novel risk stratification tools in STEMI patients with preserved LVEF.

Cardiac magnetic resonance (CMR) imaging allows unique in vivo assessments of—even discrete—functional and morphological myocardial tissue abnormalities in the setting of STEMI.[6,7] Late gadolinium-enhanced (LGE) imaging enables detection of myocardial and microvascular injury with the highest sensitivity.[8] The development of the feature-tracking (FT) technique has recently paved the way for reliable determination of myocardial strain by CMR, displaying not only global but also regional myocardial dysfunctions.[9] Thus, myocardial strain measures have been suggested as a more sensitive prognosis marker than LVEF post-STEMI.[9]

The objective of the present study was to comprehensively investigate the prognostic value of clinical risk factors, myocardial and microvascular injury, as well as myocardial strain by CMR in a large STEMI population with preserved LVEF following primary PCI.

METHODS

Study design and patient population

The STEMI population of this multicentre, individual patient-data analysis derived from two large CMR trials: the MARINA-STEMI (Magnetic Resonance Imaging In Acute ST-Elevation Myocardial Infarction, NCT04113356) trial[10] and the AIDA STEMI (Abciximab Intracoronary versus intravenously Drug Application in ST-Elevation Myocardial Infarction, NCT00712101) trial.[11] Study protocols of the two trials have been published in detail previously.[10,11] A final population of 1247 patients was analysed for the present study. A detailed flow diagram is shown in *Figure 1*.

The trials received approval by the responsible research ethics committees and were conducted in conformity with the Declaration

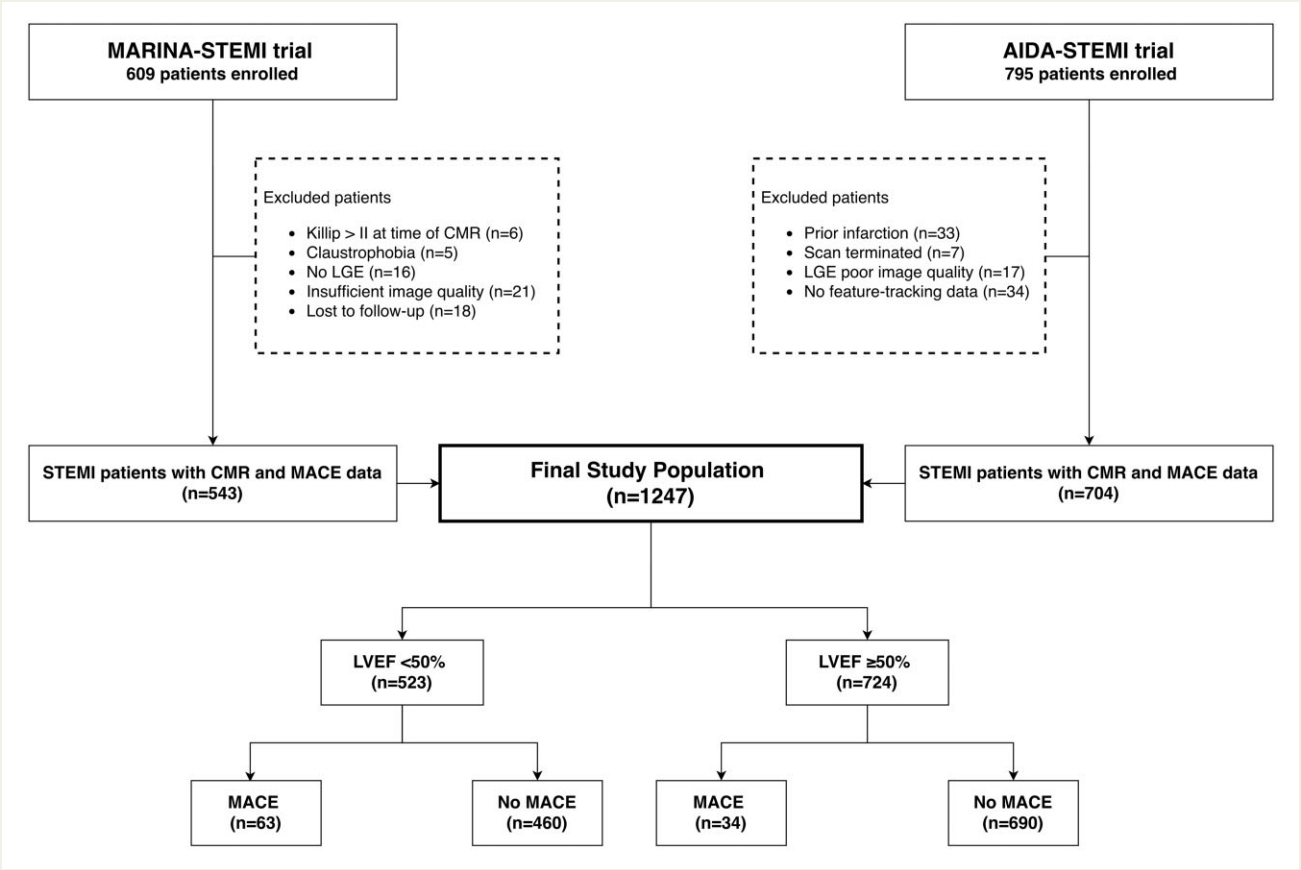


Figure 1 Flow diagram of the present study. AIDA, Abciximab Intracoronary versus intravenously Drug Application in ST-Elevation Myocardial Infarction; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MARINA, Magnetic Resonance Imaging In Acute ST-Elevation Myocardial Infarction; STEMI, ST-elevation myocardial infarction.

of Helsinki. All patients gave written informed consent prior study inclusion.

Endpoint definition

Primary endpoint of the study was the occurrence of MACE, predefined as composite of all-cause mortality, re-infarction, and new congestive heart failure.[10,11] In case a patient experienced more than one MACE event, we pre-specified the following ranking to ensure that each patient contributed only once to the composite endpoint: all-cause mortality > re-infarction > heart failure.[11] Detailed endpoint definition was reported previously.[10,11] Re-infarction was defined in accordance with contemporary guidelines as symptoms of ischaemia and/or new significant ST-segment changes with an increase in biomarkers of myocardial injury (creatine kinase-MB, troponin) above the reference limit in patients whose values had normalized, or increase of at least 50% in patients with non-normalized values. Heart failure was defined as new clinical evidence of cardiac decompensation (including cardiogenic shock, pulmonary oedema, congestion on chest radiograph, rales more than one-third from lung base, dyspnoea with oxygen saturation <90% in patients without lung disease) requiring treatment with diuretic agents or any congestive heart failure that necessitated hospital readmission.[10,11] The median follow-up time in the AIDA STEMI trial was 12 [interquartile range (IQR) 12–12] months, in the MARINA-STEMI trial 13 (IQR 8–44) months. Endpoints were assessed via telephone interview using a standardized questionnaire.

Cardiac magnetic resonance

Cardiac magnetic resonance examinations were performed on 1.5 or 3 T scanners following standardized imaging protocols.[10,11]

For the assessment of left ventricular (LV) volumes and function, standard steady-state free precession techniques were applied.[11] Short-axis stacks were used for the quantification of LVEF. Myocardial strain measurements were performed on short- and long-axis views as reported in detail previously.[10,11] Global longitudinal strain (GLS), global radial strain (GRS), and global circumferential strain (GCS) were ascertained. Good to excellent intra- and inter-observer reproducibility was observed in both trials.[10,12]

Late gadolinium enhancement images were acquired approximately 15 min after injection of a gadolinium-based contrast agent.[10,11] 'Hyper-enhancement' was defined as +5 standard deviations above the signal intensity of remote myocardium in the opposite segment of the left ventricle.[13] Late gadolinium enhancement was measured on consecutive short-axis slices and infarct size was presented as a percentage of LV myocardial mass.[14] Microvascular obstruction (MVO) was defined as persisting area of 'hypo-enhancement' within

the infarct region. The presence and extent of MVO as a percentage of total LV myocardial mass were assessed.[8,15]

Cardiac magnetic resonance core laboratories performed image analyses blinded to all clinical data.[11]

Statistical analyses

Continuous data were presented as median with IQR, categorical variables as numbers with percentages. Differences in continuous variables between two groups were evaluated by the Mann–Whitney *U*-test; differences in categorical variables between groups by χ^2 square test. Univariable and multivariable Cox regression analyses were used to disclose significant and independent predictors of MACE. Determinants of MACE from *Table 2* showing a *P*-value of <0.10 (and infarct size) were further included into multivariable Cox regression analysis. Based on the number of events, two multivariable Cox regression models (clinical Model A and CMR Model B) were formed. All independent MACE determinants from Models A and B were further incorporated into the final Cox regression Model C. The discriminative power of continuous variables for the prediction of MACE was evaluated by receiver operating characteristic (ROC) analysis. Area under the curve (AUC) values were compared by a nonparametric method established by DeLong *et al.*[16] In accordance with Rice and Harris,[17] AUC values were interpreted as negligible (≤0.55), small (0.56–0.63), moderate (0.64–0.70) and strong (≥0.71). The optimal cut-off values for the prediction of MACE were identified by Youden Index.[18] To provide a risk stratification tool in clinical practice, we created a risk score including all independent clinical (female gender and TIMI risk score) and CMR predictors (GLS and MVO) of MACE. After dichotomization of TIMI risk score and GLS at optimal cut-off (Youden Index), 1 point was assigned for each variable, resulting in a scoring range from 0 to 4 points (*Figure 2*). Subsequently, the following risk classes were formed: low (0–1 points), intermediate (2 points), and high (3–4 points). MACE-free survival was displayed by the Kaplan–Meier curve and differences were assessed by log-rank test.

IBM SPSS Statistics 25.0 (Armonk, NY, USA), MedCalc 15.8 (Ostend, Belgium), and R 3.6.1 (The R Foundation, Austria) were used for statistical calculations. A two-tailed *P*-value of <0.05 was considered as statistically significant for all tests.

RESULTS

Total study population

An overall cohort of 1247 STEMI patients treated by primary PCI was analysed. The baseline characteristics of these 1247 patients are shown in *Table 1*. Median age was 59 (IQR 51–69) years and the total ischaemic time was 187 (IQR 117–328) min. Cardiac magnetic resonance scans were conducted 3 (IQR 2–4) days after PCI for STEMI.

Patients with preserved left ventricular ejection fraction

From the 1247 patients included, 724 patients (=58%) showed a preserved LVEF defined as ≥50%. *Table 1* depicts the baseline characteristics of this patient group compared to the patients with reduced LVEF. Patients with preserved LVEF were more frequently female ($P = 0.01$), had a lower TIMI risk score ($P < 0.001$), shorter ischaemic times ($P = 0.001$) and lower peak CK concentrations ($P < 0.001$). Preserved-LVEF patients presented with the culprit lesion location in the right coronary artery ($P < 0.001$) more often and showed a higher pre- and post-interventional TIMI flow ($P < 0.001$ and 0.03, respectively). Furthermore, patients with preserved LVEF had significantly better myocardial strain indices (GLS, GRS, and GCS), a smaller overall infarct size, and lower rates as well as smaller MVO (all $P < 0.001$).

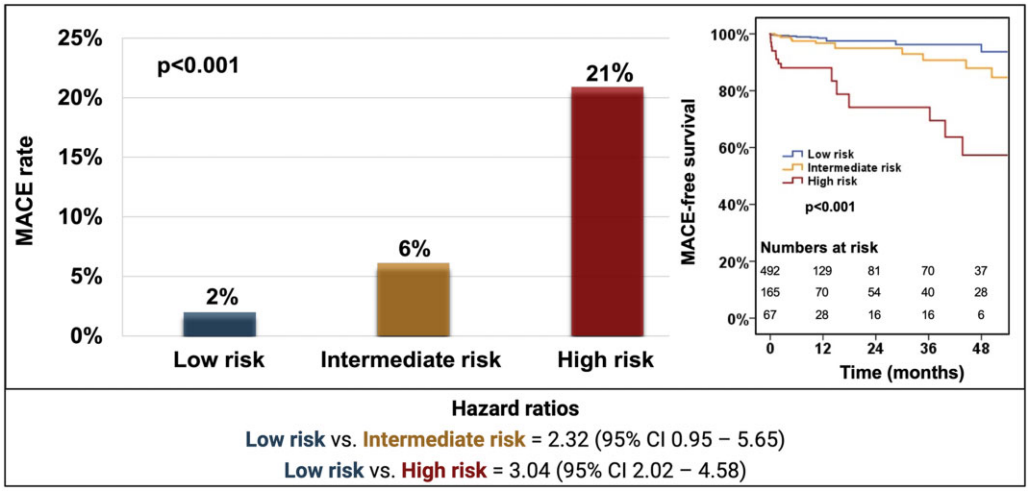


Figure 2 Prognostic stratification in STEMI patients showing a preserved LVEF. The stepwise increase of MACE rates with higher risk classes is illustrated by the bar graph. The MACE-free survival according to the different risk classes is illustrated by the Kaplan–Meier curve. CI, confidence interval; MACE, major adverse cardiovascular events.

Table 1 Patient characteristics

	Overall population ($n = 1247$)	LVEF ≥50% ($n = 724$, 58%)	LVEF <50% ($n = 523$, 42%)	*P*-value
Age (years)	59 (51–69)	59 (51–69)	59 (51–69)	0.94
Female, *n* (%)	260 (21)	170 (24)	90 (17)	0.01
Body mass index (kg/m^2)	26.8 (24.7–29.4)	26.8 (24.7–29.4)	26.7 (24.7–29.4)	0.89
Hypertension, *n* (%)	751 (60)	424 (59)	327 (63)	0.17
Current smoker, *n* (%)	601 (48)	356 (49)	245 (47)	0.38
Hyperlipidaemia, *n* (%)	574 (46)	340 (47)	234 (45)	0.38
Diabetes mellitus, *n* (%)	193 (16)	107 (15)	86 (16)	0.42
TIMI risk score	3 (2–5)	3 (2–4)	4 (2–5)	<0.001
Total ischaemic time (min)	187 (117–328)	177 (108–299)	200 (125–343)	0.001
Culprit lesion, *n* (%)				<0.001
RCA	520 (42)	377 (52)	143 (27)	
LAD	565 (45)	247 (34)	318 (61)	
LCX	158 (13)	98 (14)	60 (12)	
LM	4 (0.3)	2 (0.3)	2 (0.4)	
Number of affected vessels, *n* (%)				0.08
1	709 (57)	431 (60)	278 (53)	
2	349 (28)	189 (26)	160 (31)	
3	189 (15)	104 (14)	85 (16)	
TIMI flow pre-PCI, *n* (%)				<0.001
0	747 (60)	394 (54)	353 (68)	
1	162 (13)	92 (13)	70 (13)	
2	206 (16)	143 (20)	63 (12)	
3	132 (11)	95 (13)	37 (7)	
TIMI flow post-PCI, *n* (%)				0.03
0	21 (2)	10 (1)	11 (2)	
1	26 (2)	10 (1)	16 (3)	
2	106 (8)	53 (7)	53 (10)	
3	1094 (88)	651 (90)	443 (85)	
Peak CK (U/L)	1767 (875–3126)	1315 (637–2142)	2816 (1605–4304)	<0.001
CMR parameters				
LVEF (%)	52 (44–58)	57 (53–62)	43 (37–46)	<0.001
LVGLS (%)	−13.7 (−17.4 to −10.7)	−15.4 (−19.5 to −12.6)	−11.0 (−14.1 to −8.5)	<0.001
LVGRS (%)	23.0 (17.6–29.2)	26.1 (20.6–31.6)	19.3 (14.4–24.0)	<0.001
LVGCS (%)	−17.5 (−24.5 to −13.8)	−20.5 (−27.6 to −14.9)	−15.3 (−20.1 to −11.7)	<0.001
IS, % of LVMM	15.8 (8.3–24.4)	11.2 (5.3–17.5)	23.5 (16.1–32.1)	<0.001
MVO, *n* (%)	624 (50)	247 (34)	377 (72)	<0.001
MVO, % of LVMM	0.0 (0.0–1.9)	0.0 (0.0–0.7)	1.4 (0.0–4.2)	<0.001

CK, creatine kinase; CMR, cardiac magnetic resonance; IS, infarct size; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main artery; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVGCS, left ventricular global circumferential strain; LVGLS, left ventricular global longitudinal strain; LVGRS, left ventricular global radial strain; LVMM, left ventricular myocardial mass; MVO, microvascular obstruction; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.

Clinical outcome in patients with preserved left ventricular ejection fraction

In total, 97 patients (8%) experienced a MACE event (29 deaths, 37 re-infarctions, and 31 heart failure events) during a median follow-up time of 12 (IQR 12–13) months (18 patients were lost to follow-up, *Figure 1*). In the patient group with preserved LVEF, 34 MACE events (5%) occurred (9 deaths, 13 re-infarctions, and 12 heart failure events), the MACE rate in the patient group with reduced LVEF was 12% ($P < 0.001$).

The association between clinical characteristics and MACE in the patients with preserved LVEF is shown in *Table 2*. Patients who developed a MACE event were older ($P = 0.01$) and more frequently female ($P = 0.004$). Furthermore, patients with MACE had antecedent hypertension more frequently ($P = 0.03$) and showed a higher TIMI risk score ($P < 0.001$). Regarding CMR parameters, GLS ($P = 0.006$), and presence ($P = 0.009$) as well as extent ($P = 0.05$) of MVO were significantly associated with MACE.

The results of the multivariable Cox regression analysis are presented in *Table 3*. In 'Model A' including clinical variables, female

Table 2 Prediction of major adverse cardiovascular events in patients with preserved left ventricular ejection fraction

	HR (95% CI)	*P*-value
Age	1.04 (1.01–1.07)	0.01
Female	2.72 (1.37–5.41)	0.004
Body mass index	1.04 (0.96–1.14)	0.34
Hypertension	2.51 (1.09–5.76)	0.03
Current smoker	0.58 (0.29–1.16)	0.12
Hyperlipidaemia	0.61 (0.30–1.22)	0.16
Diabetes mellitus	1.55 (0.64–3.76)	0.33
TIMI risk score	1.33 (1.14–1.56)	<0.001
Total ischaemic time	1.00 (1.00–1.00)	0.60
Culprit lesion	1.17 (0.76–1.79)	0.48
Number of affected vessels	1.41 (0.91–2.18)	0.12
TIMI flow pre-PCI	0.83 (0.59–1.19)	0.32
TIMI flow post-PCI	0.95 (0.55–1.64)	0.85
Peak CK	1.00 (1.00–1.00)	0.60
CMR parameters		
LVEF	1.01 (0.96–1.07)	0.62
LVGLS	1.34 (1.04–1.25)	0.006
LVGRS	0.97 (0.93–1.01)	0.11
LVGCS	1.03 (0.98–1.09)	0.24
IS	1.02 (0.98–1.05)	0.36
MVO presence	2.50 (1.26–4.96)	0.009
MVO extent	1.12 (1.00–1.26)	0.05

CI, confidence interval; CK, creatine kinase; CMR, cardiac magnetic resonance; HR, hazard ratio; IS, infarct size; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main artery; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVGCS, left ventricular global circumferential strain; LVGLS, left ventricular global longitudinal strain; LVGRS, left ventricular global radial strain; LVMM, left ventricular myocardial mass; MACE, major adverse cardiovascular events; VO, microvascular obstruction; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.

gender and TIMI risk score emerged as independent predictors of MACE. In the CMR 'Model B', only GLS and the presence of MVO were independently associated with MACE. Also the associations of GLS and presence of MVO with MACE remained significant after adjustment for female gender and TIMI risk score ('Model C').

Receiver operating characteristic analysis revealed an AUC of 0.59 (95% CI 0.56–0.63) for female gender, 0.63 (95% CI 0.60–0.67) for TIMI risk score, 0.69 (95% CI 0.66–0.72) for GLS, and 0.63 (95% CI 0.59–0.67) for MVO. The optimal cut-off value of GLS was −13.3% and of TIMI risk score was 4 points. The created risk score including female gender, TIMI risk score (>4 points), GLS (>−13.3%), and presence of MVO was significantly ($P < 0.001$) associated with MACE: 0 points 1.5% MACE, 1 point 2.4% MACE, 2 points 6.1% MACE, 3 points 18.3% MACE, and 4 points 42.9% MACE. The significant ($P < 0.001$) increase in MACE rates in relation to the derived risk classes (low risk 2.0%, intermediate risk 6.1%, and high risk 20.9%) is depicted in *Figure 2*. The MACE-free survival of patients in the different score classes is illustrated by the Kaplan–Meier curve in *Figure 2*.

C-statistics revealed that the addition of the CMR predictors (GLS and MVO) to the clinical predictors (female gender and TIMI risk score) resulted in a significantly ($P = 0.02$) higher AUC [0.76 (95% CI 0.73–0.79)] compared to the clinical predictors alone [AUC 0.65 (95% CI 0.62–0.69) *Figure 3*].

In an exploratory analysis, we evaluated the potential influence of renin-angiotensin system (RAS) inhibitors at hospital discharge in patients with preserved LVEF. The vast majority of patients with preserved LVEF received RAS blockers (95%, 687 of 724 patients). In the patient subgroup with the presence of MVO and reduced GLS ($n = 102$), RAS blocker prescription was associated with a significantly lower MACE rate as compared to the patients without RAS blockers (11% vs. 63% MACE, $P < 0.001$).

DISCUSSION

This large multicentre analysis evaluated the prognostic validity of clinical risk factors, myocardial injury markers, and myocardial deformation as determined by comprehensive CMR imaging in STEMI patients with preserved LVEF following primary PCI.

The main findings were the following: (1) in STEMI patients treated by contemporary PCI, the majority of patients (58%) showed a preserved LVEF soon after PCI. (2) The absolute number of MACE events in the STEMI group with preserved LVEF was substantial ($n = 34$, 35% of all MACE events; according incidence rate 5% versus 12% in the patient group with reduced LVEF). (3) Among all CMR parameters assessed, GLS and MVO emerged as significant and independent predictors of MACE in the LVEF-preserved STEMI population.[4] Importantly, the prognostic value of GLS and MVO was incremental to clinical prognosis markers (TIMI risk score and gender) in this patient population.

These observations highlight the prognostic usefulness of MVO as a distinct marker of severe reperfusion injury and GLS as a sensitive marker of myocardial function in patients with preserved LVEF after PCI for acute STEMI. A comprehensive CMR imaging approach incorporating MVO and GLS assessment might be useful in identifying STEMI patients at increased risk of MACE, despite preserved LVEF. Whether STEMI patients with preserved LVEF but the presence of MVO and reduced GLS benefit from specific interventions warrants further investigation.

Risk stratification of ST-elevation myocardial infarction patients with preserved left ventricular ejection fraction

Non-invasive cardiac imaging is the clinical cornerstone for prognosis assessment of STEMI patients.[19] Due to its fast and broad availability, echocardiography remains the preferred imaging modality in daily clinical routine.[19] However, CMR provides higher accuracy and reproducibility in terms of quantification of LV volumes and function than echocardiography.[20] Furthermore, CMR enables advanced myocardial tissue characterization with a precise assessment of infarct size and microvascular injury in the setting of STEMI.[6] As such, CMR offers particularly high potential to better characterize the patient group with preserved LVEF.[6] However, only one small study published by Galea *et al.*[21] specifically investigated the prognostic relevance of CMR imaging in this patient population. In 77 LVEF-preserved STEMI patients treated by primary PCI, they demonstrated MVO, in particular MVO extent, as a significant determinant of long-

Table 3 Multivariable prediction of major adverse cardiovascular events in patients with preserved left ventricular ejection fraction

	Univariable		Multivariable	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Model A				
Age	1.04 (1.01–1.07)	0.01		
Female	2.72 (1.37–5.41)	0.004	2.24 (1.10–4.57)	0.03
Hypertension	2.51 (1.09–5.76)	0.03		
TIMI risk score	1.33 (1.14–1.56)	<0.001	1.28 (1.02–1.59)	0.03
Model B				
LVGLS	1.34 (1.04–1.25)	0.006	1.12 (1.02–1.23)	0.02
IS	1.02 (0.98–1.05)	0.36	–	–
MVO presence	2.50 (1.26–4.96)	0.009	2.39 (1.05–5.46)	0.04
MVO extent	1.12 (1.00–1.26)	0.05	–	–
Model C				
Female	2.72 (1.37–5.41)	0.004	2.73 (1.34–5.55)	0.01
TIMI risk score	1.33 (1.14–1.56)	<0.001	1.29 (1.09–1.51)	0.002
LVGLS	1.34 (1.04–1.25)	0.006	1.13 (1.04–1.23)	0.01
MVO presence	2.50 (1.26–4.96)	0.009	2.33 (1.16–4.66)	0.02

CI, confidence interval; HR, hazard ratio; IS, infarct size; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; MACE, major adverse cardiovascular events; MVO, microvascular obstruction; TIMI, thrombolysis in myocardial infarction.

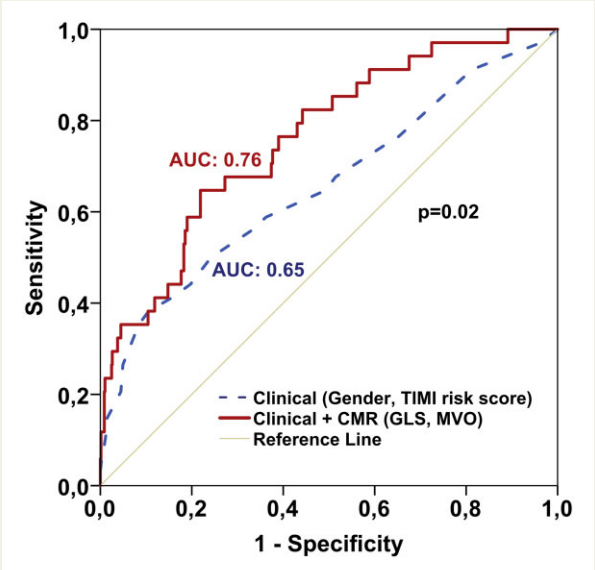


Figure 3 Discriminative power of prognosis markers in STEMI with preserved LVEF. Receiver operating characteristic analysis which compares the prognostic value of clinical prognostic markers (TIMI risk score and female gender, blue dotted line) with the combined variable incorporating the clinical markers plus CMR markers (GLS and MVO, red line). CMR, cardiac magnetic resonance; GLS, left ventricular global longitudinal strain; LVEF, left ventricular ejection fraction; MVO, microvascular obstruction; STEMI, ST-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

term outcome, whereas other CMR markers such as LV volumes, LVEF, and infarct size were not significantly related to MACE.[21] The present study analysed an LVEF-preserved STEMI population almost 10 times larger and could confirm that established CMR prognosis markers including LVEF and infarct size do not provide prognostic significance in this STEMI group. In line with Galea *et al.*, MVO, however, was significantly associated with clinical outcomes in LVEF-preserved patients. Interestingly, not extent but the presence of MVO emerged as an independent determinant of MACE in multivariable analysis. This finding may be explained by both the relatively small MVO areas in this patient population and the high proportion of patients without MVO. Nevertheless, the prognostic value of the binary variable (presence or absence of MVO) was affirmed to be independent of and incremental to clinical prognostic markers (TIMI risk score, female gender), emphasizing the clinical usefulness of MVO determination for better risk stratification of LVEF-preserved STEMI patients. As mentioned above, the study by Galea *et al.*[21] and the present analysis showed that the prognostic relevance of LVEF per se completely dissolves in patients with preserved LVEF, explainable by the fact that LVEF reflects only global LV dysfunction whereas more subtle, regional dysfunctions cannot be depicted.[2] The limited prognostic value of LVEF has also been highlighted in the clinical setting of chronic coronary syndrome.[22] The assessment of myocardial deformation by strain imaging incorporates information of both global and regional LV dysfunction and has therefore been proposed as a more sensitive prognosis marker than LVEF, with particular potential in STEMI patients showing preserved LVEF.[2] We for the first time specifically appraised the prognostic value of strain measures by FT-CMR in LVEF-preserved STEMI survivors and revealed GLS as a strong and

independent predictor of MACE in this patient group. These results again emphasize the predominant prognostic relevance of GLS post-STEMI, which, from a pathophysiological point of view, most likely be explained by the 'wavefront phenomenon'[23] and the predominantly longitudinal orientation of the subendocardial fibres.[2] Although limited in terms of imaging accuracy, GLS can also be determined by echocardiography. In addition, previous studies have demonstrated the usefulness of GLS by echocardiography for risk stratification after STEMI, even in the subgroup with preserved LVEF.[24] Thus, when CMR is not available, echocardiography-based GLS may be used for better risk assessment post-STEMI.

Clinical implications

Our findings suggest that an integrative approach including clinical risk factors (TIMI risk score and gender) and imaging information on myocardial deformation (GLS) and myocardial tissue pathology (MVO) is likely the most informative for identifying high-risk STEMI patients despite preserved LVEF. More accurate identification of these high-risk patients with normal LVEF may allow closer follow-up as well as more individualized therapies to be applied. In an exploratory analysis, we revealed a significant association between RAS blocker prescription at hospital discharge and MACE in the LVEF-preserved group at high risk (presence of MVO and reduced GLS). This analysis was limited by the retrospective nature, small group size, and by the fact that the continuation of this medication post-discharge remained unclear. However, such treatment strategies should be further evaluated by future randomized trials. Moreover, of potential future interest is, for example, the value of comprehensive CMR evaluation for improved risk evaluation of sudden cardiac death, which currently relies exclusively on LVEF to decide for transient or permanent defibrillator therapy.[25] A possible combination of CMR with other upcoming prognosis markers in this research field, for example, electrophysiological markers, would be of particular interest.[26,27] Dedicated prospective randomized trials are, however, necessary before using CMR as a risk and treatment stratification tool in clinical routine.

Limitations

Although the present pooled analysis represents the largest CMR study on LVEF-preserved STEMI patients so far, MACE rates were relatively low, which must be considered when interpreting the results of the multivariable analysis. Novel CMR mapping sequences (native and post-contrast T1 mapping, T2 and T2* mapping)[28,29] show promise for more detailed myocardial tissue characterization and prognostication post-STEMI; however, for the present study these sequences were not available. Apart from creatine kinase, other biochemical markers were not systematically available in both trials and therefore cannot be reported.

CONCLUSION

In STEMI patients undergoing primary PCI, the majority of patients showed a preserved LVEF. The absolute number of MACE events in this LVEF-preserved patient group could be affirmed to be substantial. CMR imaging with the determination of MVO and GLS provided strong prognostic validity that was independent of and incremental to established clinical prognosis markers, suggesting an important role for a CMR-based risk prediction approach in STEMI survivors with preserved LVEF.

Lead Author Biography

Martin Reindl is currently working as a resident at the Department of Cardiology at the Medical University of Innsbruck. After graduating from medical school with honors (University of Innsbruck), he obtained his PhD degree under the supervision of Prof. Bernhard Metzler and Dr. Sebastian J. Reinstadler. His research focuses on the pathophysiology of myocardial infarction and the development of novel tools for risk stratification of patients with infarction. The present analysis is based on a research collaboration with Dr. Stiermaier and Prof. Eitel (Lübeck) as well as with Dr. Feistritzer and Prof. Thiele (Leipzig).

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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